

Multiple sclerosis

Authors: Doctors Dorothée Chabas¹ and Bertrand Fontaine,
Professor Olivier Lyon-Caen
Creation Date: December 2002
Update: July 2004

Scientific Editor: Professor Alexis Brice

¹Fédération de Neurologie, Hôpital Salpêtrière, Bâtiment Paul Castaigne 47-83 Bd de l'Hôpital, 75013 Paris, France. dorothee.chabas@psl.ap-hop-paris.fr

[Abstract](#)
[Keywords](#)
[Disease name and synonyms](#)
[Excluded diseases](#)
[Definition/Diagnostic criteria](#)
[Clinical features](#)
[Treatment](#)
[Physiopathology](#)
[Diagnostic methods](#)
[Genetic counseling](#)
[MS and pregnancy](#)
[Unresolved questions](#)
[References](#)

Abstract

Multiple sclerosis [MS] is an autoimmune and inflammatory demyelinating disease of the central nervous system, affecting 0.25-6 individuals in 1000. It is often characterized by relapsing episodes of neurologic impairment followed by remissions (relapsing remitting MS). In about a third of MS patients the disease evolves into a progressive course (secondary progressive MS). In a minority of patients progressive neurologic deterioration without remission occurs from the disease onset (primary progressive MS). Genetic and environmental factors influence susceptibility to the disease, but MS is not a genetically inherited condition. MS diagnosis is based on clinical and radiological criteria (Magnetic Resonance Imaging [MRI]). In some cases a lumbar puncture and other non invasive investigations might also be needed. Disabling relapses are treated with intravenous injections of high doses of corticosteroids. In relapsing remitting MS, immunomodulatory treatments like interferon beta and copolymer reduce the risk of relapses. These treatments are administered by injections at least once a week. Immunosuppressors might also be used in aggressive forms of the disease, most of the time intravenously. Physical therapy plays a key role in the management of MS disability. Depending on the symptoms (tremor, spasticity), other specific medication might be indicated. The pathological mechanism underlying MS is regarded as an autoimmune attack of the myelin sheat, mediated by both cellular and humoral immunity, and recent data have suggested that MS is also a degenerative disease affecting axons and oligodendrocytes.

Keywords

Multiple sclerosis, Inflammation, Central nervous system, Autoimmunity, T cells, Cytokines, Interferon beta, Copolymer, MRI, Cerebrospinal fluid.

Disease name and synonyms

Multiple sclerosis

Excluded diseases

At the onset, MS may be mistaken for other inflammatory diseases of the central nervous system, such as [Behcet disease](#),

[antiphospholipid syndrome](#), or acute disseminated encephalomyelitis (ADEM). Pseudotumoral MS may be reminiscent of lymphoma, other tumors (glial tumors), or infectious diseases (like Lyme disease, HTLV1 infection, abscess). Recurrent relapses of neurologic impairment may also be mistaken for cavernomatosis. In most cases, MRI findings, cerebrospinal fluid analysis, evoked potentials, the association with systemic signs and the relapsing remitting evolution allow exclusion of other diagnosis. Brain biopsy is needed only exceptionally.

Definition/Diagnostic criteria

Multiple sclerosis [MS] is an autoimmune and inflammatory demyelinating disease of the central nervous system, affecting 0.25-6 ‰ of general population. It is often characterized by relapsing episodes of neurologic impairment followed by remissions. MS diagnostic criteria have been recently updated (Mc Donald *et al*, 2001). On the basis of these criteria, an individual is usually classified either as having MS, or possible MS, or as not having MS.

Clinical features

MS onset usually occurs in young adulthood, and the female to male ratio is 2:1. MS is often characterized by relapsing episodes of neurologic impairment followed by remissions, and this is called relapsing remitting MS (85-90%). The first relapse usually consists of optic neuritis (20-30%), acute myelitis (20-50%), or brainstem lesions (10-15%). Inaugural sensory symptoms can be sometimes mistaken for non-neurological symptoms. Optic neuritis is typically characterized by a rapidly progressive unilateral loss of vision, associated with pain when moving the eyeball. Ophthalmoscopic examination is usually normal during the acute phase. Myelitis may manifest as sensory symptoms like tingling sensation of the limbs, associated with motor deficiency. Brainstem lesions may induce oculomotor troubles, facial weakness and sensory symptoms like face hypoaesthesia or pain. In relapsing remitting MS, patients usually recover totally from the first relapse in a few weeks. Further relapses may occur, sometimes after a few months, or more than ten years later (mean 2.5 years). These relapses may be characterized by other clinical features, like cerebellar symptoms (ataxia) and urinary troubles. Cognitive impairment may also occur, disturbing attention span and concentration. Some patients do not recover totally and suffer from disabling and remaining sequelae of their relapses. Other patients (10-30%) develop

“benign MS” with no significant disability after 10 years of disease evolution. However, the disease may evolve into a secondary progressive course after a few years (30% at 5 years, 90 % at 25 years), with or without relapses. The progressive course leads to progressive disability, with approximately 25-35% of patients presenting with walking disabilities after 10 years of disease evolution. Finally approximately 10-15 % of MS patients have a primary progressive course from the disease onset, without any relapse. The sex-ratio in this group is slightly different (1/1), patients tend to be older, and are mainly affected by chronic myelitis. No test is currently available to predict disease evolution in a given patient. It has not been established whether relapsing and progressive MS are distinct disorders.

Treatment

Treatment of relapses

Disabling relapses may be treated with high doses of intravenous corticosteroids (for example methylprednisolone 1g/day for 3 days). In some cases, like in severe optic neuritis, this treatment might be followed by a tapering dose of oral corticotherapy for 2-3 weeks. Small doses of oral corticotherapy are not effective in MS. In addition, a study about optic neuritis has even shown that the relapse rate after oral corticotherapy alone is higher than in the placebo group. Treatment with intravenous methylprednisolone is based on the experience of neurologists treating MS patients, but its benefits have never been clearly demonstrated in a double blinded clinical trial versus placebo. It seems however that it shortens the course of relapse and improves disability, but with no effect on the natural history of the disease. In view of the risks involved, corticosteroids treatment of mild relapses might not be indicated.

MS drugs

In the last 10 years, two main immunomodulatory drugs have demonstrated their efficiency as disease modifying therapies in MS: interferon beta and copolymer. Both drugs reduce the relapses rate by approximately 30%, and have also a significant effect on MRI lesions (reduction in the number of new gadolinium-enhanced lesions and total burden of T2 lesions). Their efficacy in preventing the apparition and evolution of the disability remains discussed. No controlled study has been performed for more than 5 years. The mechanisms of action of both drugs are different: interferon beta binds to receptors located on the

surface of immune cells, and decreases Th1 proinflammatory activation, whereas copolymer binds to T-cell receptors in a specific way, and deviates the autoimmunity targeted against myelin epitopes by production of autoreactive regulator Th2 cells (bystander suppression). Interferon beta and copolymer are usually well tolerated. However, some side effects may be associated with interferon and include mainly local cutaneous intolerance to injections, flulike symptoms after injections, and sometimes leucopenia and hepatotoxicity.

Neither interferon beta nor copolymer have proven their efficiency in primary progressive MS. In these MS forms, other immunoregulatory treatments and immunosuppressive drugs have been tested, such as monthly bolus therapy of cyclophosphamide or methylprednisolone, oral methotrexate, oral azathioprine, plasmapheresis, and intravenous polyclonal Ig. Although none of these drugs have ever been tested in a reproducible way in double blinded trials versus placebo, they might be valuable in particular cases, especially those presenting with a rapidly progressive course that leads to severe disability in a short period of time (worsening MS). In these particular cases, the potential therapeutic efficiency of these immunosuppressors is thought to overcome their potential side effects (*i.e.* immunodepression with a higher risk of infection, and teratogenicity). Mitoxantrone is another immunosuppressive drug, initially used in chemotherapy, that might be helpful in aggressive worsening MS, but its indication is limited given its potential cardiac side effect (cardiac deficiency) and carcinogenic effects (leukemia). Patients treated with all these immunosuppressive drugs should be carefully monitored by MS specialists.

Symptomatic treatment

Physiotherapy plays a key role in MS management by reducing spasticity, preventing retractions, and helping MS patients to live with disability on a daily basis (ataxia, motor deficiency). Adjuvant treatments (propranolol, primidone, piracetam) might also be given to help managing cerebellar tremor and some neurosurgical treatments might even be suggested in very severe cases. Myorelaxant drugs (baclofene, dantrolene) can be used to treat spasticity, and a releasing pump (delivering myorelaxant medication on a continuous basis) might be sometimes implanted. Amantadine might be proposed in the morning to improve fatigue, which is a very common symptom in MS. Urinary and fecal troubles can be very disabling, and require symptomatic treatments, such as

alfuzosine, oxybutynine, depending on the type of trouble. In some cases, urinary catheterization might be indicated. Prevention is primordial in disabled patients: mobilization is needed for avoiding bedsores, and special diet (and sometimes gastrostomy) is indicated if deglutition is impaired, in order to avoid pulmonary infection. Depression should be carefully detected and treated by psychotherapy and/or medication, when required. The social repercussions of the disease on work and family life should be taken into consideration.

Physiopathology

Multiple sclerosis is a demyelinating and inflammatory disease of the central nervous system, of unknown origin. The physiopathological mechanism underlying MS is regarded as an autoimmune attack of the myelin sheath, mediated by both cellular and humoral immunity. Autoreactive T cells have been particularly well studied in MS, because plaque formation is mainly mediated by T cells, especially T helper cells (CD4+). These T cells produce Th1 cytokines such as interleukine 12 or interferon gamma and interact with MHC class II molecules which are upregulated in MS brain. In addition, the role of autoreactive T cells in the disease has been demonstrated in the experimental animal model of MS by induction of experimental autoimmune encephalomyelitis (EAE) upon injection of autoreactive T cells alone. Upon costimulation -mediated by costimulatory molecules such as B7 and CD28- autoreactive T cells recognize the autoantigen myelin peptide through the T cell receptor (TCR). The encephalogenic T cells, which express adhesion molecules like VLA-4, bind to endothelial cells expressing ligands to these adhesion molecules (like ICAM-1), traverse the blood brain barrier to enter the central nervous system, migrate through the extracellular matrix where metalloprotease activation can be detected, and induce lesions.

Plaques formation is mediated by inflammatory cells, mainly T cells, macrophages, and sometimes B cells. Complement might also be involved. Local demyelination occurs, with an up regulation of inducible nitric oxide synthetase, local inflammation and production of Th1 cytokines, while Th2 cytokines correlate with remissions. Myelin damage induces a local release of myelin peptides, leading to a cascade of autoimmune reactions called epitope spreading.

Recent data have suggested that MS is not only an inflammatory disease of the myelin sheath, but also a degenerative disease affecting axons and

maybe oligodendrocytes. Pathological studies have also suggested that MS is an heterogeneous entity, and that different clinical types of MS can be distinguished according to the type of cells seen in the plaques and the characteristics of demyelinating lesions.

Diagnostic methods

There is no specific diagnosis test for MS. The diagnosis can only be ascertained by pathological analysis, but brain biopsy is generally not required, except for some particular cases such as pseudotumoral MS.

MS diagnosis is based on the objective evidence of lesions disseminated in space and time, and the exclusion of other possible diseases according to the symptomatology. Clinical features, MRI findings and other supportive examinations (cerebrospinal fluid analysis and visual evoked potentials) contribute to the diagnostic process. MS diagnostic guidelines have been recently updated (Mc Donald criteria, 2001), and categorize patients into either "MS", "possible MS" and "not MS". Early diagnosis of MS allows early treatments by immunomodulators, when indicated.

Magnetic Resonance Imaging (MRI)

In typical MS, brain MRI shows lesions (plaques) disseminated in the white matter. Some of them are or have been symptomatic (relapse), although most of them are clinically silent. Globally the number of lesions observed is 5-20 times higher than the number of clinical relapses. The lesion burden correlates more or less with the duration of the disease. The lesions are mainly located in periventricular white matter. Infratentorial and juxtacortical lesions are also very suggestive of the diagnosis. These lesions are hyper intense on T2-weighted and FLAIR images. On T1-weighted images, the gadolinium-enhanced lesions reflect a blood-brain-barrier leakage and correspond to recent and active lesions, whereas older lesions appear as rather isointense or hypo intense signals. Lesions seen in MRI may demonstrate MS criteria of dissemination in space (Barkhof criteria, 1997), and when MRI is repeated with at least a 3 months interval, changes in lesion burden may also fulfill MS criteria of dissemination in time. Finally, spinal cord MRI may provide additional findings consistent with MS criteria of dissemination in space since it is abnormal in approximately 70% of patients (T2 hyper intense signal of myelopathy). In conclusion, MRI is a key diagnostic tool for MS.

Other supportive examinations

Cerebrospinal fluid

Cerebrospinal fluid [CSF] is collected by lumbar puncture for analysis. Cytological examination confirms the inflammatory process when 35% of samples contain more than 5 lymphocytes/mm³ (and less than 1% with more than 50 cells/mm³). An increase of the protein concentration, usually under 1g/l, is indicative of a blood-brain-barrier breakdown, similarly to an increase of the albumin ratio ($Q\text{ Alb} = \frac{[\text{Alb}]_{\text{CSF}}}{[\text{Alb}]_{\text{serum}}}$) above 7×10^{-3} (12% of the patients).

Immunoglobulin (IgGs) analysis shows an intrathecal IgG synthesis in most patients. The IgG index ($= \frac{Q\text{ IgG}}{Q\text{ Alb}}$) is increased in 70-80 % of MS patients. Isoelectric focusing with matched serum/CSF samples allows a qualitative analysis of the IgG profile, and shows that 95% of MS patients have more IgG bands in CSF than in serum. This "oligoclonal profile of the CSF" supports the occurrence of an inflammatory process in the CSF, and constitutes a positive diagnostic criteria highly suggestive of MS. However, it is not a feature specific to MS, as it can be detected in many inflammatory, infectious and tumoral diseases of the CNS.

Evoked potentials

Evoked potentials provide a non invasive technique for analyzing different neurological pathways which may be impaired in MS, besides MRI normality (argument for dissemination in space). Visual evoked potentials may indicate electrical abnormalities of the optic nerve, which are suggestive of an old or infraclinical optic neuritis. Brainstem and sensory evoked potentials may reveal lesions of the auditory and the spinal cord sensory pathways, respectively.

Genetic counseling

MS is not a genetically inherited disorder, since no gene has been found to be specifically impaired in MS patients, and the disease is not associated with monogenic transmission of any type. However, MS is a multifactorial disease, influenced by environmental and genetic factors. The role of environmental factors has been supported by the observation that susceptibility to MS is higher in Nordic populations than in populations living near the Equator. Genetic contribution has been suggested by the existence of multiplex families (families with at least two members suffering from MS, 10-15%), the higher risk in first degree relatives of MS patients to develop the disease (20-40 fold higher), and the higher MS concordance rate in monozygote twins (6-40%) than in dizygote twins

(2.7-4.7%). In addition, genetic studies have demonstrated the influence of the MHC (Major Histocompatibility Complex) on MS susceptibility; for example, in Northern Europe, MS is associated with HLA DRB1*1501. However, these observations have no direct and obvious influence on genetic counseling for MS patients. There is no prenatal diagnostic test for MS. Given the intrafamilial variability of MS phenotype, it is impossible to predict whether all members would be similarly affected within the same family.

MS and pregnancy

Although MS does not influence fertility, MS relapse rate is globally lower during the last trimester of pregnancy, whereas relapses are more frequent during the first 3 months of post partum. Methylprednisolone bolus might be given if a severe MS relapse occurs during pregnancy. Breastfeeding has no proven influence on the risk of post partum relapse. MS does not interfere with delivery and is not a contraindication to epidural anaesthesia. Although no side effect has been reported, it is recommended to discontinue interferon beta and copolymer treatments 3 months before pregnancy. Female patients treated with methylprednisolone should be aware that it temporarily lowers IUD contraception efficiency, whereas it should not influence oral contraception.

Unresolved questions

Etiologic mechanisms underlying MS are not well known. The immunological changes occurring during MS are extensively described, but the primary cause of the disease is still unknown, and the degenerative participation has been barely explored. The efficiency of interferon beta and copolymer on the relapse rate is significant, but only by 30%. Moreover, time is needed to evaluate the tolerance to these treatments and their long-term efficiency on persistent disability. Meanwhile, clinical trials regarding relapsing remitting MS are actively ongoing.

They investigate the effects of new immunomodulatory drugs antigen specific drugs (like altered peptide ligands APLs), or non antigen specific drugs. Some authors are studying combinations of drugs that are already used in MS monotherapy. Treatments aiming to repair the myelin sheath, or drugs targeting progressive MS, are still under preliminary investigation. Many other aspects involved in MS are debated, like the influence of vaccination on the disease course. To our knowledge, there are not any data reported as yet demonstrating a specific epidemiological or a pathophysiological relation between hepatitis B vaccination and MS. However, as a general rule in MS patients, hepatitis vaccination is not recommended unless otherwise indicated (professional exposure or risk factors of contamination).

References

- Barkhof F**, Filippi M, Miller DH, Scheltens P, Campi A, Polman CH, Comi G, Ader HJ, Losseff N, Valk J. Comparison of MRI criteria at first presentation to predict conversion to clinically definite multiple sclerosis. *Brain*, 120:2059-69 (1997).
- Ebers G**, Wekerle H, Lassmann H, Matthews B, McDonald I. *Mc Alpine's Multiple Sclerosis*. 3rd edition. Churchill Livingstone (1998).
- Edan G**, Morrissey S, Le Page E. Rationale for the use of mitoxantrone in multiple sclerosis. *J Neurol Sci*, 223:35-9 (2004).
- Fernandez O**, Fernandez V, De Ramon E. Azathioprine and methotrexate in multiple sclerosis. *J Neurol Sci*, 223:29-34 (2004).
- Gonsette RE**. Pixantrone (BBR2778): a new immunosuppressant in multiple sclerosis with a low cardiotoxicity. *J Neurol Sci*, 223:81-6 (2004).
- Hommes OR**, Weiner HL. Clinical practice of immunosuppressive treatments in multiple sclerosis; results of a second international questionnaire. *J Neurol Sci*, 223:65-7 (2004).
- Jeffery DR**. The argument against the use of cyclophosphamide and mitoxantrone in the treatment of multiple sclerosis. *J Neurol Sci*, 223:41-6 (2004).
- Matejuk A**, Bakke AC, Hopke C, Dwyer J, Vandenberg AA, Offner H. Estrogen treatment induces a novel population of regulatory cells, which suppresses experimental autoimmune encephalomyelitis. *J Neurosci Res*, 77:119-26. (2004).
- McDonald WI**, Compston A, Edan G, Goodkin D, Hartung HP, Lublin FD, McFarland HF, Paty DW, Polman CH, Reingold SC, Sandberg-Wollheim M, Sibley W, Thompson A, van den Noort S, Weinshenker BY, Wolinsky JS. Recommended diagnostic criteria for multiple

sclerosis: guidelines from the International Panel on the diagnosis of multiple sclerosis. *Ann Neurol*, 50:121-7 (2001).

Patti F, Amato MP, Filippi M, Gallo P, Trojano M, Comi GC. A double blind, placebo-controlled, phase II, add-on study of cyclophosphamide (CTX) for 24 months in patients affected by multiple sclerosis on a background therapy with interferon-beta study denomination: CYCLIN. *J Neurol Sci*, 223:69-71 (2004).

Steinman L. Multiple sclerosis: a coordinated immunological attack against myelin in the central nervous system. *Cell*, 85:299-302 (1996).

Steinman L. Multiple sclerosis: a two-stage disease. *Nat Immunol*, 2:762-4. (2001).

Trapp BD et al. Axonal transection in the lesions of multiple sclerosis. *N Engl J Med*, 338: 278-85 (1998).

Weiner HL. Immunosuppressive treatment in multiple sclerosis. *J Neurol Sci* 22:1-11 (2004).