

Multiple sclerosis: a short review of the disease and its differences between men and women

Keywords

Multiple sclerosis
Review
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Birgit Reipert

Abstract

Multiple sclerosis (MS) is an inflammatory disease of the CNS that is characterized by a demyelination of axons in inflammatory plaques which leads to a deficiency or complete loss in the transmission of nerve impulses.

The majority of patients have either relapsing remitting multiple sclerosis (RRMS) or secondary progressive MS (SPMS). Both forms affect women more than men; the female to male ratio is about 2:1. This difference in the susceptibility to these forms of MS is probably due to sex hormones. Animal studies have shown that testosterone is protective against the disease.

Patients with MS can experience partial or complete loss of any function that is controlled by the CNS. Depending on which areas of the CNS are affected and how badly they are damaged, the type and severity of symptoms can vary greatly. The diagnosis of MS is based on long-established clinical parameters and the exclusion of any other disease that might cause similar symptoms. Over the last 10 years magnetic resonance imaging (MRI) has played an increasingly important role in the diagnostic process.

Multiple sclerosis cannot be cured but there are treatments both to slow down the course of the disease and to treat the symptoms. Current research activities in MS will eventually lead to new treatment strategies that might involve a combination of immunomodulation, remyelination and neuroprotection.

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What is multiple sclerosis and how is it caused ?

Multiple sclerosis (MS) was first described by Charcot and Vulpian in 1866 [1]. MS is an inflammatory disease of the Central Nervous System (CNS). The inflammation causes patches of damage called plaques or lesions that are predominantly located in the white matter of the CNS. At the site of an inflammatory lesion the myelin sheath gets lost in a process called demyelination. When the myelin is lost, the transmission of nerve impulses is slowed or even stopped. To some extent, the myelin sheath around the axons can be repaired after

the inflammation has resolved. This process is called remyelination and is triggered by oligodendrocytes. If there are not enough oligodendrocytes present at the site of the lesion, remyelination may not take place or only happen partially. In this case, the nerve will continue to function in an abnormal way, but the axon might remain undamaged for a long time. The lost myelin can also be replaced with scar tissue, which gave MS its name: “multiple” many and “sclerosis” scar forming. Once axons have become scarified they do not fully regain their former function.

As the disease progresses, oligodendrocytes and, ultimately, the axons themselves are

Birgit Reipert, PhD
Baxter BioScience,
Vienna, Austria

E-mail:
birgit_reipert@baxter.com

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destroyed, which leads to a worsening of disease symptoms. There is overwhelming evidence that the destruction is caused by the body's own immune system indicating that MS is an autoimmune disease.

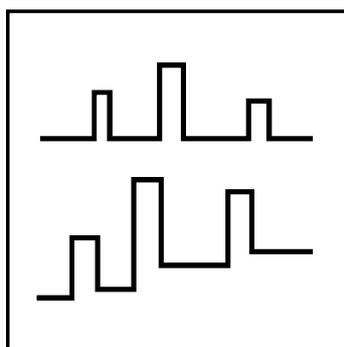
Different types of multiple sclerosis

There are three internationally recognized forms of MS: relapsing/remitting multiple sclerosis (RRMS), primary progressive multiple sclerosis (PPMS) and secondary progressive multiple sclerosis (SPMS).

Relapsing/remitting multiple sclerosis (RRMS)

Most people presenting with MS (about 80%) are first diagnosed with relapsing/remitting MS (RRMS). In this form, patients experience a series of relapses (also known as exacerbations) followed by complete or partial disappearance of the symptoms (remissions) until another relapse occurs. There can be weeks to decades between relapses. Relapses can last for days, weeks or months and recovery can be slow and gradual or almost instantaneous. During remission the patient fully or partially recovers from the deficits acquired during the relapse.

The following graph, showing level of disability over time, demonstrates two typical courses of RRMS (www.mult-sclerosis.org).

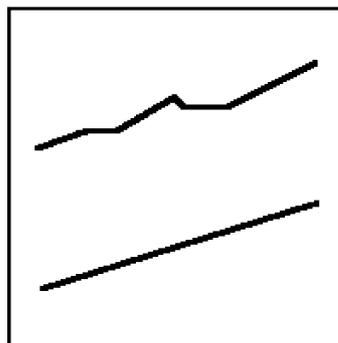


Primary progressive multiple sclerosis (PPMS)

About 10–20% of people presenting with MS suffer from primary progressive MS (PPMS). This form is characterized by a gradual progression of the disease involving a decline in the patient's physical abilities with only short

periods where the decline seems to stop with some minor relief.

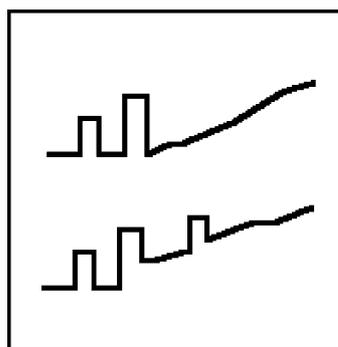
The following graph, showing level of disability over time, demonstrates two typical courses of PPMS (www.mult-sclerosis.org).



Secondary progressive multiple sclerosis (SPMS)

About 50% of MS patients who are first diagnosed as having RRMS will develop SPMS within 10 years. By 25 to 30 years, that figure will have risen to 90%. The SPMS form is characterized by a steady progression of clinical neurological damage with or without superimposed relapses and minor remissions and plateaus. Any superimposed relapses and remissions tend to tail off over time. The SPMS form tends to be associated with less formation of inflammatory lesion than RRMS but the total burden of disease continues to progress. This is believed to be caused by higher levels of axonal loss.

The following graph, showing level of disability over time, demonstrates two typical courses of SPMS (www.mult-sclerosis.org).



Multiple sclerosis: the differences between men and women

In RRMS and SPMS, MS affects women more than men; the female to male ratio is about

2:1 [2]. Whereas the onset of MS in woman tends to be early (ages 18 to 30), the onset of MS in men tends to be later in life (ages 30 to 40). Young men are relatively protected from disease, which appears to be due at least in part to a protective effect of testosterone [3]. The onset of MS in men coincides with the beginning of the decline in bioavailable testosterone in healthy men [3]. Studies in animal models of MS have shown that treatment of male and female mice with testosterone ameliorated the disease [3]. Implications for a possible therapy of MS patients were that very high doses of testosterone would be needed for effective treatment of woman with MS. Such high levels would not be well tolerated in the long term in woman due to masculinizing side effects [3]. However, supplemental testosterone therapy might be considered as a possible therapy for men with MS [3].

The amelioration of the disease in woman during the third trimester of pregnancy is another gender issue in MS. High levels of the pregnancy hormone estriol appear to contribute to the disease protection during this time. Studies in animal models found that mice treated with estriol have less severe disease than mice treated with placebo control [3]. In a pilot clinical trial, oral estriol treatment of patients with RRMS significantly decreased inflammatory lesions of the brain and improved immunological factors [4].

The form of PPMS has a different sex ratio from other forms of the disease. Men are as much at risk of getting PPMS as women [2].

Symptoms of multiple sclerosis

In principal, people with MS can experience partial or complete loss of any function that is controlled by the CNS. Depending on which areas of the CNS are affected and how badly they are damaged, the type and severity of symptoms can vary greatly.

The RRMS type typically starts with sensory disturbances, unilateral optic neuritis, diplopia (internuclear ophthalmoplegia), Lhermitte's sign (trunk and limb parathesias evoked by neck flexion), limb weakness, clumsiness, gait ataxia, and neurological bladder and bowel symptoms [2]. Many patients suffer from fatigue, which is worse in the afternoon and is accompanied by physiologic increases in body

temperature [2]. Some patients have recurring brief, stereotypical phenomena (paroxysmal pain or paresthesias, trigeminal neuralgia, episodic clumsiness or dysarthria and tonic limb posturing) that are highly suggestive of MS [2].

Patients who have PPMS often present with a slowly evolving upper-motor-neuron syndrome of the legs ("chronic progressive myelopathy"). Typically, this form of MS worsens gradually, and quadriplegia, cognitive decline, visual loss, brain-stem syndromes, and cerebellar, bowel and sexual dysfunction can develop [2].

Diagnosis of multiple sclerosis

There are no laboratory tests, symptoms, or physical findings that can, by themselves, determine if a person has multiple sclerosis. Moreover, there are many symptoms of MS that can also be caused by other diseases. Therefore, the MS diagnosis can only be made by carefully ruling out all other possibilities.

The long-established criteria for diagnosing MS are (www.nmss.org/doc):

1. There must be objective evidence of two relapses (i.e. two episodes of demyelination in the CNS). A relapse, also known as an exacerbation or flare, is defined clinically as the sudden appearance or worsening of an MS symptom or symptoms, which lasts for at least 24 hours and up to about 1 month. The objective evidence comes from findings on the neurologic exam and additional tests.
2. The two relapses must be separated in time (at least 1 month apart) and space (indicated by evidence of inflammation or damage or both in different areas of the CNS).
3. There must be no other explanation for these relapses or the symptoms the patient is experiencing.

Over the last 20 years, tests such as magnetic resonance imaging (MRI), examination of cerebrospinal fluid, and evoked response testing have played an increasingly important role in the diagnostic process. In 2001 the International Panel on the Diagnosis of Multiple Sclerosis issued a revised set of diagnostic criteria [5]. In addition to the traditional requirements, the revision provides specific

guidelines for using findings on MRI, cerebrospinal fluid analysis, and visual evoked potentials to provide evidence of the second relapse and thereby confirm the diagnosis more quickly. These guidelines also facilitate the diagnostic process in those patients who have had steady progression of disability without distinct relapses.

The MRI test is the preferred method of imaging the brain to detect the presence of plaques or scarring caused by MS. This technology is able to detect lesions in different parts of the CNS and differentiate old lesions from those that are new or active. Unlike computerized tomography (CT) or conventional X-ray, the MRI scan does not use radiation. Instead, it uses magnetism and radio waves. Powerful magnetic fields interact with the hydrogen atoms found in the water contained in all body tissues and fluids. Radio frequency signals cause these hydrogen atoms to release energy, and computers translate the changes into cross-sectional images. The scanning procedure is very sensitive, and can often

create pictures of lesions, or areas of damage, that would be missed by a CT scan (www.nmss.org/doc).

The degree of disability of patients with MS is quantified by the so-called Kurtzke Expanded Disability Status Scale (EDSS, [6]). The EDSS quantifies disability in eight functional systems (FS) and allows neurologists to assign a Functional System Score (FSS) in each of these. The functional systems are:

- pyramidal
- cerebellar
- brainstem
- sensory
- bowel and bladder
- visual
- cerebral
- other

The EDSS steps 1.0 to 4.5 refer to people with MS who are fully ambulatory. EDSS steps 5.0 to 9.5 are defined by the impairment to ambulation.

Kurtzke Expanded Disability Status Scale

- 0.0 Normal neurological examination
- 1.0 No disability, minimal signs in one FS
- 1.5 No disability, minimal signs in more than one FS
- 2.0 Minimal disability in one FS
- 2.5 Mild disability in one FS or minimal disability in two FS
- 3.0 Moderate disability in one FS, or mild disability in three or four FS. Fully ambulatory
- 3.5 Fully ambulatory but with moderate disability in one FS and more than minimal disability in several others
- 4.0 Fully ambulatory without aid, self-sufficient, up and about some 12 hours a day despite relatively severe disability; able to walk without aid or rest some 500 meters
- 4.5 Fully ambulatory without aid, up and about much of the day, able to work a full day, may otherwise have some limitation of full activity or require minimal assistance; characterized by relatively severe disability; able to walk without aid or rest some 300 meters.
- 5.0 Ambulatory without aid or rest for about 200 meters; disability severe enough to impair full daily activities (work a full day without special provisions)
- 5.5 Ambulatory without aid or rest for about 100 meters; disability severe enough to preclude full daily activities
- 6.0 Intermittent or unilateral constant assistance (cane, crutch, brace) required to walk about 100 meters with or without resting
- 6.5 Constant bilateral assistance (canes, crutches, braces) required to walk about 20 meters without resting
- 7.0 Unable to walk beyond approximately five meters even with aid, essentially restricted to wheelchair; wheels self in standard wheelchair and transfers alone; up and about in wheelchair some 12 hours a day
- 7.5 Unable to take more than a few steps; restricted to wheelchair; may need aid in transfer; wheels self but cannot carry on in standard wheelchair a full day; May require motorized wheelchair
- 8.0 Essentially restricted to bed or chair or perambulated in wheelchair, but may be out of bed itself much of the day; retains many self-care functions; generally has effective use of arms
- 8.5 Essentially restricted to bed much of day; has some effective use of arms retains some self care functions
- 9.0 Confined to bed; can still communicate and eat.
- 9.5 Totally helpless bed patient; unable to communicate effectively or eat/swallow
- 10.0 Death due to MS

Treatment of multiple sclerosis

Currently there is no cure for MS but there are treatments both to slow down the course of the disease and to treat the symptoms of MS. Drugs that are able to modify the course of the disease are called disease-modifiers. Three groups of disease-modifiers have been approved for the treatment of MS: interferon beta, Glatiramer acetate and Mitoxantrone, a chemotherapeutic agent.

Interferon (IFN) beta

Three interferon beta medications have been approved for treating relapsing forms of MS: i.m. IFN beta-1a (Avonex from Biogen); s.c. IFN beta-1a (Rebif from Ares-Serono) and s.c. IFN beta-1b (Betaseron from Berlex, Betaferon from Schering);

Avonex, manufactured by Biogen, is a form of beta interferon known as interferon beta-1a for intramuscular application. It is identical to the naturally occurring protein found in the human body. Avonex is used to modify the course of MS. Avonex has been shown in clinical trials to reduce the average relapse rate in people with the RRMS and SPMS forms of the disease [7–10].

Rebif, manufactured by Ares-Serono, is the same substance as Avonex but injected subcutaneously. Similar to Avonex, Rebif has been shown in clinical trials to reduce the average relapse rate in people with the RRMS and SPMS forms of the disease [11–14].

Betaseron (known as *Betaferon* in Europe) is manufactured by Schering and its US associate Berlex. It is injected subcutaneously and has been shown to reduce average relapse rate in people with the RRMS and SPMS forms of the disease [11,12,15,16].

Glatiramer acetate

Glatiramer acetate is a random chain polypeptide containing the amino acids glutamic acid, lysine, alanine and tyrosine (GLATiramer). It was originally designed to mimic a protein in myelin, called myelin basic protein, with the intention of inducing experimental autoimmune encephalomyelitis (an animal model of MS). However, it was found to suppress the disease and was trialed in human MS. Copaxone, manufactured by Teva Marion Partners is the brand name for glatiramer acetate. In early trials of the drug, it was known as Copolymer-1 and Cop-1. Copaxone has been

shown in clinical trials to reduce the average relapse rate in people with the RRMS form of the disease and to limit the formation of new lesions in the CNS [17–19].

Mitoxantrone

Mitoxantrone (Novantrone, from Ares-serono), a synthetic anthracenedione derivative, is an antineoplastic, immunomodulatory agent. Its presumed mechanism of action in patients with MS is via immunomodulatory mechanisms, although these remain to be fully explained. Intravenous mitoxantrone treatment improved neurological disability and delayed progression of MS in patients with the PRMS and SPMS forms of the disease [20–22].

The standard treatment for significant acute exacerbations is the use of steroids, which exert powerful anti-inflammatory effects. Steroids reduce inflammation at the site of new demyelination, allowing return to normal function to occur more rapidly and reducing the duration of the exacerbation. The current favoured steroid regimen is methyl-prednisolone given intravenously in high doses for 3–5 days with, perhaps, subsequent tapering lower oral doses of prednisone for 1–2 weeks. The use of steroids are not thought to have any effect on the long-term course of the disease (www.msif.org/doc).

Epidemiology of multiple sclerosis

The prevalence of MS varies considerably around the world [23]. Kurtzke classified regions of the world according to prevalence: a low prevalence corresponds to 5 cases of MS per 100,000 inhabitants; an intermediate prevalence corresponds to 5–30 cases of MS per 100,000 inhabitants and a high prevalence corresponds to more than 30 cases of MS per 100,000 inhabitants [24]. The prevalence is highest in Northern Europe, Southern Australia and the middle part of North America [2]. The reasons for the variation in prevalence are not fully understood. Both environmental and genetic factors are currently discussed [2].

Current areas of research in multiple sclerosis

Over the last year, there have been over 1,500 articles published in medical journals on

MS or animal models of the disease (www.multiple-sclerosis.org). Most important research activities are currently focused on the following areas: genetics of MS susceptibility, importance of environmental factors in the development of MS, factors that trigger the disease, regulation of the autoimmune component in MS, demyelination and remyelination of axons, biology of nerve cells.

Genetics of MS susceptibility and importance of environmental factors in the development of MS

Recently, there has been a lot of interest in the genetics of complex diseases such as multiple sclerosis. The human genome has been mapped in its entirety, which will allow researchers to isolate the genes associated with such diseases by statistical analysis of affected populations. MS is known to cluster in some families and the risk of the disease is significantly increased for people who have close family members with the disease. People with MS have a 10% to 20% chance of having one or more affected relatives, which is much higher than one would expect for a disease that had no genetic component. Moreover, MS is significantly more common in certain racial groups (white northern Europeans) than others, even when controlling for latitude (another risk factor). However, it is known that genetic factors are not the only risk factors of MS. People with identical genes (i.e. identical twins) both have MS in only 25% to 30% of cases [25,26]. Such data show that MS is not a classic genetic disease in the way that sickle cell anaemia, cystic fibrosis or Huntington's disease are – people with these diseases always have a particular genetic configuration and people with that configuration always get the disease. With MS, there must be some, as yet unknown, environmental factor that also contributes to the risk of contracting multiple sclerosis.

Factors that trigger the disease and factors that regulate the autoimmune component in MS

Understanding the pathophysiology of MS is essential for the development of better treatment strategies. Currently we know that MS is an inflammatory, demyelinating disease of the CNS. The cause of the disease, however,

is unknown. There is a body of evidence suggesting that the disease is due to myelin-specific autoreactive T cells, activated in the periphery, which cross the blood-brain barrier because of an overexpression of chemokines [27,28]. These autoreactive T cells could drive the inflammatory process in the white matter of the CNS. The question remains, what stimulus is responsible for the activation of these autoreactive T cells in the periphery? Some data suggests that viruses such as human herpesvirus type 6 are involved in this process [29]. One of the major sources of tissue damage in the CNS seems to be activated macrophages that produce several inflammatory products such as cytokines, reactive oxygen and nitric oxide. Furthermore, autoantibodies that are able to activate the complement system might be involved in tissue damage [30]. A central question in understanding the pathophysiology of nervous damage in MS is the role of inflammation and the relation between inflammation, demyelination and axonal degeneration.

Demyelination and remyelination of axons and biology of nerve cells

Demyelination is the pathological hallmark of MS lesions. The concept of remyelination has gained acceptance in recent years, but naturally occurring remyelination is incomplete. To improve repair processes, a number of strategies have been explored experimentally and clinical trials are being carried out [31]. In principle, remyelination can be achieved by either promoting endogenous repair mechanisms or by providing an exogenous source of myelinating cells via transplantation. Both approaches have been successful in animal models of demyelination. Additionally, many studies have explained principal mechanisms of oligodendrocyte biology and remyelination in the CNS [31]. Unfortunately, the translation of these experimental data into clinical treatments has proved difficult. More information on the pathogenesis of MS, the reason why repair mechanisms fail in MS and a better understanding of the regulation of remyelination is required. This will ultimately lead to a specific treatment tailored for the individual patient and will probably involve a combination of immunomodulation, remyelination and neuroprotection [32].

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