

# Multiple Sclerosis

## What is multiple sclerosis?

Multiple sclerosis (MS) is a central nervous system disorder in which nerve cells lose their insulating sheath, called myelin. Nerves are able to regenerate their myelin sheath, but its destruction in MS is so rapid that the nerve may die before regeneration can occur. This results in the appearance of plaques (sclera) in the brain and spinal cord, in which nerve cells are replaced by fibrous connective tissue.

Clinical symptoms depend on the location of the damage, but can include vision loss or double vision, speech difficulties, muscular weakness, abnormal skin sensations, bladder problems, fatigue, pain and mood alterations. The disease typically shows exacerbations and remissions, although there is often a general worsening over time. Magnetic resonance imaging (MRI) is a sensitive diagnostic technique that can be used to measure its progress.

The cause of MS is unknown and its progress cannot be predicted with certainty. No infectious agent has been definitely linked to MS, but the immune system is thought to be involved in the inflammation that accompanies myelin destruction. A peculiarity of MS is that its evolution cannot be anticipated and varies from one person to another.

Two distinct patterns are generally recognised. At diagnosis, about 15 per cent of those affected have *primary chronic progressive* MS (CP-MS) and 85 per cent have *relapsing-relapsing* MS (RR-MS). Over time, about half of the RR-MS patients develop a *secondary progressive* form (SP-MS). In RR-MS, neurological problems appear suddenly, followed by slow improvement. About 15-20 per cent of these patients relapse within the first year: the shorter the time to relapse, the poorer the prognosis. In CP-MS, the deterioration is gradual and the intervals of remitted disease are absent.

## Who does MS affect?

MS is estimated to affect around 650,000 people in the European Union, with a higher incidence and prevalence in northern Europe, and typically strikes young adults in their 20s and 30s. It is more common in women than in men by a ratio of 3:2.

Two types of evidence support the connection between heredity and susceptibility to MS: The first comes from population studies. People from different ethnic groups have different tendencies to develop the disease. The other evidence comes from studies of families in which MS occurs more frequently than chance would dictate. The average person in Europe has about one chance in 750 of developing MS. Relatives of people with MS, such as children, siblings or non-identical twins, have a chance rang-

**Multiple Sclerosis is a disease of the central nervous system. The insulating sheath around the nerves is progressively destroyed. This leads to a variety of distressing symptoms. It typically strikes young adults. The cause is still unknown. New approaches to treatment are being tested including antibody therapies and a factor which may help nerve-regeneration. Hopefully, future therapies for this devastating disease will be more than just palliative.**



ing from one in 100 to one in 40. The identical twin of someone with MS has a one in three chance of developing the disease.

### **Present treatments:**

The main medications used to treat acute exacerbations of MS have traditionally been anti-inflammatory steroids. These reduce the duration and severity of acute attacks, but there is no evidence that they are useful in the progressive form of MS, or that they alter the long-term course of the relapsing type of MS, and their possible adverse effects (skin reactions, weight gain, osteoporosis, mood alterations) make them unsuitable for prolonged use.

For the management of other symptoms, centrally active muscle relaxants or tranquillisers may be given to reduce muscular spasms. Anticholinergic medicines can be helpful to treat MS patients for the complications of the urinary tract.

Newer treatments for RR-MS include forms of recombinant beta interferon. They are all given by injection and reduce the frequency and severity of attacks in RR-MS, although not everyone responds to them. They are, however, not a cure for the disease and may cause flu-like symptoms in some people.

Interferon beta is also used for treatment of the secondary progressive form of MS. Data from Phase 3 studies show varying effects on the progression of disability in this form of MS, although clinical benefits have been seen. A topoisomerase II inhibitor, given by injection, has also been approved for the treatment of worsening RR-MS.

A macromolecular compound recently introduced for the treatment of RR-MS is believed to work by a quite different mechanism from beta interferons. The compound is thought to mimic the protein component of the nerve's myelin sheath and act as a decoy during acute attacks by immune system cells (T-lymphocytes), which damage myelin. It reduces the frequency and severity of relapses to a similar extent to beta interferon and is given by daily subcutaneous injection. Adverse reactions may include redness and pain at the injection site, flushing, chest pain, muscle weakness and nausea.

The most recently introduced medication for RR-MS is a monoclonal antibody for those patients who have not responded to treatment with beta interferon. The compound has been shown to be highly effective in reducing disability progression, the rate of relapses and the number of new or enlarging brain lesions. The medicine is given by intravenous infusion and because its use has been associated with an increased risk of a potentially fatal opportunistic viral infection of the brain, it may not be used in those at increased risk for such infection.

### **What's in the development pipeline?**

Although the cause of MS is still unknown, research continues to seek improved disease-modifying and supportive therapies. Compounds are in development for all types of MS. Two research groups are studying a monoclonal antibody preparation that has been shown to reduce the formation of new brain lesions in MS patients suffering from the primary progressive form. The antibody binds to alpha-4-integrin receptors on the surface of lymphocytes and may stop them migrating into the brain to cause new lesions.

Most research is focused on the relapsing-remitting form of MS. Researchers are studying an oral compound which lowers the number of circulating activated T-cells and which has demonstrated a reduction in relapse rate. Another potential disease-modifying agent for MS is a monoclonal anti-interleukin (IL)-12 antibody. IL-12 is known to help activate T-cells that can cause tissue damage and the antibody might therefore be able to reduce the nerve cell destruction seen in MS. Investigators are also

studying the effects of a human monoclonal antibody that is directed against B lymphocytes. This project is in clinical Phase 2.

There are recent results of a randomized Phase 2 clinical trial with a monoclonal antibody that binds to cells of the immune system which are considered to be involved in the pathogenesis of RR-MS. The antibody has been shown to reduce number of relapses and to demonstrate actual improvement in scores of patients' functions. This new approach is being further evaluated in Phase 3 trials.

Supportive treatments for MS are also being actively developed and there are first positive results in clinical trials to evaluate a cannabis-based preparation (THC:CBD narrow ratio) given as a sub-lingual spray for controlling intractable pain, spasticity and bladder dysfunction in MS.

### **The longer-term future:**

Further approaches to finding a disease-modifying treatment are at an earlier stage. Approval has recently been granted for the beginning of clinical studies of a blood cell-derived human alpha interferon.

Other research laboratories are developing a means of preventing T-cells from entering the brain, based on fundamental research into the working of the blood-brain barrier. There is also work underway to developing glial cell growth factor 2 (GGF2) for the treatment of MS. This factor stimulates the cells making up the myelin sheath of nerves and may be expected to help nerve regeneration.

Repair of the myelin sheath normally occurs spontaneously, but in MS, the myelin repair process occurs very slowly or fails altogether. Researchers have recently presented results of studies with a monoclonal antibody which binds to myelin and the surface of cells in the brain and spinal cord, and triggers the cells to begin the repair process called remyelination. The antibody is the first known reagent designed to induce repair by acting within the central nervous system at the damage sites.

While these therapies are still at an early stage, there is reason to hope that future therapy for this devastating disease may be more than just palliative.



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