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Multiple Sclerosis

Multiple sclerosis (abbreviated MS, also known as disseminated sclerosis orencephalomyelitis disseminata) is an autoimmune condition in which the immune system attacks the central nervous system (CNS), leading to demyelination. It may cause numerous physical and mental symptoms, and often progresses to physical and cognitive disability. Disease onset usually occurs in young adults, is more common in women, and has a prevalence that ranges between 2 and 150 per 100,000 depending on the country or specific population. MS was first described in 1868 by Jean-Martin Charcot.

MS affects the areas of the brain and spinal cord known as the white matter. White matter cells carry signals between the grey matter areas, where the processing is done, and the rest of the body. More specifically, MS destroys oligodendrocytes which are the cells responsible for creating and maintaining a fatty layer, known as the myelin sheath, which helps the neurons carry electrical signals. MS results in a thinning or complete loss of myelin and, less frequently, the cutting (transection) of the neuron's extensions or axons. When the myelin is lost, the neurons can no longer effectively conduct their electrical signals. The name *multiple sclerosis* refers to the scars (scleroses - better known as plaques or lesions) in the white matter. Loss of myelin in these lesions causes some of the symptoms, which vary widely depending upon which signals are interrupted. However, more advanced forms of imaging are now showing that much of the damage happens outside these regions. Almost any neurological symptom can accompany the disease.

MS takes several forms, with new symptoms occurring either in discrete attacks (relapsing forms) or slowly accumulating over time (progressive forms). Most people are first diagnosed with relapsing-remitting MS but develop secondary-progressive MS (SPMS) after a number of years. Between attacks, symptoms may go away completely,

but permanent neurological problems often persist, especially as the disease advances.
Although much is known about the mechanisms involved in the disease process, the cause remains elusive: the most widely-held theory being that the condition results from attacks to the nervous system by the body's own immune system. Some believe it is a metabolically dependent disease while others think that it might be caused by a virus such as Epstein-Barr. Still others believe that its virtual absence from tropical areas points to a deficiency of vitamin D during childhood.

This disease does not have a cure, but several therapies have proven helpful. Treatments attempt to return function after an attack, prevent new attacks, and prevent disability. MS medications can have adverse effects or be poorly tolerated, and many patients pursue alternative treatments, despite the paucity of supporting scientific study. Many candidate therapies are still under investigation.

The prognosis, or expected course of the disease, depends on the subtype of the disease, the individual patient's disease characteristics, the initial symptoms, and the degree of disability the person experiences as time advances. Life expectancy of patients, however, is nearly the same as that of the unaffected population, and in some cases a near-normal life is possible.

Signs and symptoms

MS presents with a variety of symptoms, including changes in sensation (hypoesthesia), muscle weakness, abnormal muscle spasms, or difficulty in moving; difficulties with coordination and balance (ataxia); problems in speech (dysarthria) or swallowing (dysphagia), visual problems (nystagmus, optic neuritis, or diplopia), fatigue and acute or chronic pain syndromes, and bladder and bowel difficulties. Cognitive impairment of varying degrees, or emotional

symptomatology in the form of depression or pseudobulbar affect are also common. Neuropathic pain is usual, and this can be in the form of Lhermitte's sign. Neuropathic pain is the most common, distressing and intractable of the pain syndromes in MS. This pain is described as constant, boring, burning or tingling intensely. It usually occurs in the legs. Paraesthesias include pins and needles; tingling; shivering; burning pains; feelings of pressure; and areas of skin with heightened sensitivity to touch. The pains associated with these can be aching, throbbing, stabbing, shooting, gnawing, tingling, tightness and numbness. The main clinical measure of disability progression and severity of the symptoms is the Expanded Disability Status Scale or EDSS.

The initial attacks (also known as exacerbations or relapses) are often transient, mild (or asymptomatic), and self-limited. They often do not prompt a health care visit and sometimes are only identified in retrospect once the diagnosis has been made based on further attacks. The most common initial symptoms reported are: changes in sensation in the arms, legs or face (33%), complete or partial vision loss (optic neuritis) (16%), weakness (13%), double vision (7%), unsteadiness when walking (5%), and balance problems (3%); but many rare initial symptoms have been reported such as aphasia or psychosis. Fifteen percent of individuals have multiple symptoms when they first seek medical attention. Optic neuritis or focal leg weakness may lead to falls and other serious accidents. For some people the initial MS attack is preceded by infection, trauma, or strenuous physical effort.

Diagnosis

Multiple sclerosis is difficult to diagnose in its early stages. In fact, a definite diagnosis cannot be made until other disease processes (differential diagnoses) have been ruled out and, in the case of relapsing-remitting MS, there is evidence of at least two anatomically separate demyelinating events separated by at least thirty days. In the

case of primary progressive, a slow progression of signs and symptoms over at least 6 months is required.

Historically, different criteria were used and the Schumacher and Poser criteria were both popular. Currently, the McDonald criteria represent international efforts to standardize the diagnosis of MS using clinical, laboratory and radiologic data.

- Clinical data alone may be sufficient for a diagnosis of MS. If an individual has suffered two separate episodes of neurologic symptoms characteristic of MS, and the individual also has consistent abnormalities on physical examination, a diagnosis of MS can be made with no further testing. Since some people with MS seek medical attention after only one attack, other testing may hasten the diagnosis and allow earlier initiation of therapy.

- Magnetic resonance imaging (MRI) and magnetic resonance spectroscopy (MRS) of the brain and spine is often used during the diagnostic process. MRI shows areas of demyelination (lesions) as bright spots on the image. Gadolinium can be administered intravenously to highlight active plaques and, by elimination, demonstrate the existence of historical lesions not associated with clinical symptoms. This can provide the evidence of chronic disease needed for a definitive diagnosis of MS.

- Testing of cerebrospinal fluid (CSF) can provide evidence of chronic inflammation of the central nervous system. The CSF is tested for oligoclonal bands, which are immunoglobulins found in 75% to 85% of people with definite MS (but also found in people with other diseases). Combined with MRI and clinical data, the presence of oligoclonal bands can help make a definite diagnosis of MS. Lumbar puncture is the procedure used to collect a sample of CSF.

- The brain of a person with MS often responds less actively to stimulation of the optic nerve and sensory nerves. These brain responses can be examined using visual evoked potentials (VEPs) and somatosensory evoked potentials (SEPs). Decreased activity on either test can reveal demyelination which may be otherwise asymptomatic. Along with other data, these exams can help find the

widespread nerve involvement required for a definite diagnosis of MS.

Another test, which may become important in the future, is measurement of antibodies against myelin proteins such as myelin oligodendrocyte glycoprotein (MOG) and myelin basic protein (MBP). As of 2007, however, there is no established role for these tests in diagnosing MS. Optical coherence tomography of the eye's retina is also under study, mainly as a tool to measure response to medication and axonal degeneration.

The signs and symptoms of MS can be similar to other medical problems, such as neuromyelitis optica, stroke, brain inflammation, infections such as Lyme disease (which can produce identical MRI lesions and CSF abnormalities), tumors, and other autoimmune problems, such as lupus. Additional testing may be needed to help distinguish MS from these other problems.

Disease course and clinical subtypes

The course of MS is difficult to predict, and the disease may at times either lie dormant or progress steadily. Several subtypes, or patterns of progression, have been described. Subtypes use the past course of the disease in an attempt to predict the future course. Subtypes are important not only for prognosis but also for therapeutic decisions. In 1996 the United States National Multiple Sclerosis Society standardized the following four subtype definitions:

Relapsing-remitting

Relapsing-remitting describes the initial course of 85% to 90% of individuals with MS. This subtype is characterized by unpredictable attacks (relapses) followed by periods of months to years of relative quiet (remision) with no new signs of disease activity. Deficits suffered during the attacks may either resolve or may be permanent. When deficits always resolve between attacks, this is referred to as "benign" MS.

Secondary progressive

Secondary progressive describes around 80% of those with initial relapsing-remitting MS, who then begin to have neurologic decline between their acute attacks without any definite periods of remission. This decline may include new neurologic symptoms, worsening cognitive function, or other deficits. Secondary progressive is the most common type of MS and causes the greatest amount of disability.

Primary progressive

Primary progressive describes the approximately 10% of individuals who never have remission after their initial MS symptoms. Decline occurs continuously without clear attacks. The primary progressive subtype tends to affect people who are older at disease onset.

Progressive relapsing

Progressive relapsing describes those individuals who, from the onset of their MS, have a steady neurologic decline but also suffer superimposed attacks; and is the least common of all subtypes

Nevertheless the earliest clinical presentation of relapsing-remitting MS (RRMS) is the clinically isolated syndrome (CIS). In CIS, there is a subacute attack suggestive of demyelination but the person does not fulfill the criteria for multiple sclerosis. Several studies have shown that starting treatment with interferons during the initial attack can decrease the chance that a patient will develop clinical MS. Cases of MS before the CIS are sometimes found during other neurological inspections and are referred to as subclinical MS. Preclinical MS refers to cases after the CIS but before the confirming second attack.

During the standard clinical course, relapses rate decreases with disease time. Special cases of the disease with non-standard behavior have also been described although many researchers believe they are different diseases. These cases are sometimes referred to as borderline forms of multiple sclerosis and are Neuromyelitis optica (NMO), Balo concentric sclerosis, Schilder's diffuse sclerosis and Marburg multiple sclerosis.

Factors triggering a relapse

Multiple sclerosis relapses are often unpredictable and can occur without warning with no obvious inciting factors. Some attacks, however, are preceded by common triggers. In general, relapses occur more frequently during spring and summer than during autumn and winter. Infections, such as the common cold, influenza, and gastroenteritis, increase the risk for a relapse. Emotional and physical stress may also trigger an attack, as can severe illness of any kind. Statistically, there is no good evidence that either trauma or surgery trigger relapses. People with MS can participate in sports, but they should probably avoid extremely strenuous exertion, such as marathon running. Heat can transiently increase symptoms, which is known as Uhthoff's phenomenon. This is why some people with MS avoid saunas or even hot showers. However, heat is not an established trigger of relapses.

Pregnancy can directly affect the susceptibility for relapse. The last three months of pregnancy offer a natural protection against relapses. However, during the first few months after delivery, the risk for a relapse is increased 20%-40%. Pregnancy does not seem to influence long-term disability. Children born to mothers with MS are not at increased risk for birth defects or other problems.

Many potential triggers have been examined and found not to influence relapse rates in MS. Influenza vaccination is safe, does not trigger relapses, and can therefore be recommended for people with MS. There is also no evidence that vaccines for hepatitis B, varicella, tetanus, or Bacille Calmette-Guerin (BCG—immunization for tuberculosis) increases the risk for relapse.

Pathophysiology

Although much is known about how multiple sclerosis causes damage, the reasons why multiple sclerosis occurs are not known.

Multiple sclerosis is a disease in which the myelin (a fatty substance

which covers the axons of nerve cells) degenerates. According to the view of most researchers, a special subset of lymphocytes, called T cells, plays a key role in the development of MS.

According to a strictly immunological explanation of MS, the inflammatory process is triggered by the T cells. T cells gain entry into the brain via the blood-brain barrier (a capillary system that should prevent entrance of T-cells into the nervous system). The blood brain barrier is normally not permeable to these types of cells, unless triggered by either infection or a virus, where the integrity of the tight junctions forming the blood-brain barrier is decreased. When the blood brain barrier regains its integrity (usually after infection or virus has cleared) the T cells are trapped inside the brain. These lymphocytes recognize myelin as foreign and attack it as if it were an invading virus. That triggers inflammatory processes, stimulating other immune cells and soluble factors like cytokines and antibodies. Leaks form in the blood-brain barrier. These leaks, in turn, cause a number of other damaging effects such as swelling, activation of macrophages, and more activation of cytokines and other destructive proteins such as matrix metalloproteinases. A deficiency of uric acid has been implicated in this process.

It is known that a repair process, called remyelination, takes place in early phases of the disease, but the oligodendrocytes that originally formed a myelin sheath cannot completely rebuild a destroyed myelin sheath. The newly-formed myelin sheaths are thinner and often not as effective as the original ones. Repeated attacks lead to successively fewer effective remyelinations, until a scar-like plaque is built up around the damaged axons, according to four different damage patterns. The central nervous system should be able to recruit oligodendrocyte stem cells capable of turning into mature myelinating oligodendrocytes, but it is suspected that something inhibits stem cells in affected areas.

The axons themselves can also be damaged by the attacks. Often, the brain is able to compensate for some of this damage, due to an ability called neuroplasticity. MS symptoms develop as the cumulative result of multiple lesions in the brain and spinal cord. This is why symptoms can vary greatly between different individuals, depending on where their lesions occur.

Causes

Although many risk factors for multiple sclerosis have been identified, no definitive cause has been found. MS likely occurs as a result of some combination of both environmental and genetic factors. Various theories try to combine the known data into plausible explanations. Although most accept an autoimmune explanation, several theories suggest that MS is an appropriate immune response to one or several underlying conditions (the etiology could be heterogeneous). The need for alternative theories is supported by the poor results of present therapies, since autoimmune theory predicted greater success.

Environmental

The most popular hypothesis is that a viral infection or retroviral reactivation primes a susceptible immune system for an abnormal reaction later in life. On a molecular level, this might occur if there is a structural similarity between the infectious virus and some component of the central nervous system, leading to eventual confusion in the immune system.

A correlation between clinical MS and presence of an endogenous retrovirus called HERV has been found. The strong correlation of MS to HERV infection, suggests that MS patients might benefit from use of HERV targeted antivirals or a gene therapy strategy to neutralize the HERV infection directly.

Since MS seems to be more common in people who live farther from

the equator, another theory proposes that decreased sunlight exposure and possibly decreased vitamin D production may help cause MS. This theory is bolstered by recent research into the biochemistry of vitamin D, which has shown that it is an important immune system regulator. A large, 2006 study by the Harvard School of Public Health, reported evidence of a link between vitamin D deficiency and the onset of multiple sclerosis. Other data comes from a 2007 study which concluded that sun exposure during childhood reduces the risk of suffering MS, while controlling for genetic factors.

Other theories, noting that MS is less common in children with siblings, suggest that less exposure to illness in childhood leads to an immune system which is not primed to fight infection and is thus more likely to attack the body. One explanation for this would be an imbalance between the Th1 type of helper T-cells, which fight infection, and the Th2 type, which are more active in allergy and more likely to attack the body.

Other theories describe MS as an immune response to a chronic infection. The association of MS with the Epstein-Barr virus suggests a potential viral contribution in at least some individuals. Human endogenous retroviruses could also be involved, specially one called MSRV (MS associated retrovirus). Still others believe that MS may sometimes result from a chronic infection with spirochetal bacteria, a hypothesis supported by research in which cystic forms were isolated from the cerebrospinal fluid of all MS patients in a small study. When the cysts were cultured, propagating spirochetes emerged. Another bacterium that has been implicated in MS is *Chlamydophila pneumoniae*; it or its DNA has been found in the cerebrospinal fluid of MS patients by several research laboratories, with one study finding that the oligoclonal bands of 14 of the 17 MS patients studied consisted largely of antibodies to Chlamydophila antigens. Varicella zoster virus is also suspected to be involved.

Severe stress may also be a factor—a large study in Denmark found that parents who had lost a child unexpectedly were 50% more likely to develop MS than parents who had not. Smoking has also been shown to be an independent risk factor for developing MS.

Genetic

MS is not considered a hereditary disease. However, increasing scientific evidence suggests that genetics may play a role in determining a person's susceptibility to MS:

Some populations, such as the Roma, Inuit, and Bantus, rarely if ever develop MS. The indigenous peoples of the Americas and Asians have very low incidence rates.

In the population at large, the chance of developing MS is less than a tenth of one percent. However, if one person in a family has MS, that person's first-degree relatives—parents, children, and siblings—have a one to three percent chance of getting the disease.

For identical twins, the likelihood that the second twin may develop MS if the first twin does is about 30%. For fraternal twins (who do not inherit an identical set of genes), the likelihood is closer to that for non-twin siblings, at about 4%. This pattern suggests that, while genetic factors clearly help determine the risk of MS, other factors such as environmental effects or random chance are also involved. The actual correlation may be somewhat higher than reported by these numbers as people with MS lesions remain essentially asymptomatic throughout their lives.

Further indications that more than one gene is involved in MS susceptibility comes from studies of families in which more than one member has MS. Several research teams found that people with MS inherit certain regions on individual genes more frequently than people without MS. Of particular interest is the human leukocyte antigen (HLA) or major histocompatibility complex region on chromosome 6. HLAs are genetically determined proteins that influence the immune system. However, there are other genes in this region which are not related to the immune system.

The HLA patterns of MS patients tend to be different from those of people without the disease. Investigations in northern Europe and America have detected three HLAs that are more prevalent in people with MS than in the general population. Studies of American MS patients have shown that people with MS also tend to exhibit these HLAs in combination—that is, they have more than one of the three HLAs—more frequently than the rest of the population. Furthermore, there is evidence that different combinations of the HLAs may correspond to variations in disease severity and progression.

A large study examining 334,923 single nucleotide polymorphisms (small variations in genes) in 931 families showed that apart from HLA-DRA there were two genes in which polymorphisms strongly predicted MS; these were the *IL2RA* (a subunit of the receptor for interleukin 2) and the *IL7RA* (*idem* for interleukin 7) genes. Mutations in these genes were already known to be associated with diabetes mellitus type 1 and other autoimmune conditions; the findings circumstantially support the notion that MS is an autoimmune disease.

Studies of families with multiple cases of MS and research comparing proteins expressed in humans with MS to those of mice with EAE suggest that another area related to MS susceptibility may be located on chromosome 5. Other regions on chromosomes 2, 3, 7, 11, 17, 19, and X have also been identified as possibly containing genes involved in the development of MS.

These studies strengthen the theory that MS is the result of a number of factors rather than a single gene or other agent. Development of MS is likely to be influenced by the interactions of a number of genes, each of which (individually) has only a modest effect. Additional studies are needed to specifically pinpoint which genes are involved, determine their function, and learn how each gene's interactions with other genes and with the environment make an individual susceptible to MS.

Treatment

Although there is no known cure for multiple sclerosis, several therapies have proven helpful. The primary aims of therapy are returning function after an attack, preventing new attacks, and preventing disability. As with any medical treatment, medications used in the management of MS have several adverse effects, and many possible therapies are still under investigation. At the same time different alternative treatments are pursued by many patients, despite the paucity of supporting, comparable, replicated scientific study.

Management of acute attacks

During symptomatic attacks administration of high doses of intravenous corticosteroids, such as methylprednisolone, is the routine therapy for acute relapses. The aim of this kind of treatment is to end the attack sooner and leave fewer lasting deficits in the patient. Although generally effective in the short term for relieving symptoms, corticosteroid treatments do not appear to have a significant impact on long-term recovery. Potential side effects include osteoporosis and impaired memory, the latter being reversible.

Disease modifying treatments

Disease-modifying treatments are expensive and most of these require frequent (up-to-daily) injections. Others require IV infusions at 1-3

month intervals.

The earliest clinical presentation of relapsing-remitting MS (RRMS) is the clinically isolated syndrome (CIS). Several studies have shown that treatment with interferons during an initial attack can decrease the chance that a patient will develop MS.

As of 2007, six disease-modifying treatments have been approved by regulatory agencies of different countries for relapsing-remitting MS. Three are interferons: two formulations of interferon beta-1a (trade names *Avonex* and *Rebif*) and one of interferon beta-1b (U.S. trade name*Betaseron*, in Europe and Japan *Betaferon*). A fourth medication is glatiramer acetate (*Copaxone*). The fifth medication, mitoxantrone, is an immunosuppressant also used in cancer chemotherapy, is approved only in the USA and largely for SPMS. Finally, the sixth is natalizumab (marketed as *Tysabri*). All six medications are modestly effective at decreasing the number of attacks and slowing progression to disability, although they differ in their efficacy rate and studies of their long-term effects are still lacking. Comparisons between immunomodulators (all but mitoxantrone) show that the most effective is natalizumab, both in terms of relapse rate reduction and halting disability progression; it has also been shown to reduce the severity of MS. Mitoxantrone may be the most effective of them all; however, it is generally considered not as a long-term therapy as its use is limited by severe cardiotoxicity.

The interferons and glatiramer acetate are delivered by frequent injections, varying from once-per-day for glatiramer acetate to once-per-week (but intra-muscular) for Avonex. Natalizumab and mitoxantrone are given by IV infusion at monthly intervals.

Treatment of progressive MS is more difficult than relapsing-remitting MS. Mitoxantrone has shown positive effects in patients with a secondary progressive and progressive relapsing courses. It is moderately effective in reducing the progression of the disease and the frequency of relapses in patients in short-term follow-up. On the other hand no treatment has been proven to modify the course of primary progressive MS.

As with any medical treatment, these treatments have several adverse

effects. One of the most common is irritation at the injection site for glatiramer acetate and the Interferon treatments. Over time, a visible dent at the injection site due to the local destruction of fat tissue, known as lipoatrophy, may develop. Interferons also produce symptoms similar to influenza; while some patients taking glatiramer experience a post-injection reaction manifested by flushing, chest tightness, heart palpitations, breathlessness, and anxiety, which usually lasts less than thirty minutes. More dangerous are liver damage of interferons and mitoxantrone, the immunosuppressive effects and cardiac toxicity of the latter; or the putative link between natalizumab and some cases of progressive multifocal leukoencephalopathy in patients who had taken it in combination with interferons.

Management of the effects of MS

Disease-modifying treatments only reduce the progression rate of the disease but do not stop it. As multiple sclerosis progresses, the symptomatology tends to increase. The disease is associated with a variety of symptoms and functional deficits that result in a range of progressive impairments and handicap. Management of these deficits is therefore very important. Both drug therapy and neurorehabilitation have shown to ease the burden of some symptoms, even though neither influence disease progression. As for any patient with neurologic deficits, a multidisciplinary approach is key to limiting and overcoming disability; however there are particular difficulties in specifying a 'core team' because people with MS may need help from almost any health profession or service at some point. Similarly for each symptom there are different treatment options. Treatments should therefore be individualized depending both on the patient and the physician

Therapies under investigation

Scientists continue their extensive efforts to create new and better therapies for MS. There are a number of treatments under investigation that may improve function, curtail attacks, or limit the progression of the underlying disease. Many treatments already in clinical trials involve drugs that are used in other diseases or medications that have not been designed specifically for MS. There are also trials involving the combination of drugs that are already in use for multiple sclerosis. Finally, there are also many basic investigations that try to understand better the disease and in the future may help to find new treatments.

Alternative treatments

Different alternative treatments are pursued by many patients, despite the paucity of supporting, comparable, replicated scientific study. Examples are dietary regimens, herbal medicine, including the use of medical cannabis to help alleviate symptoms, or hyperbaric oxygenation. On the other hand the therapeutic practice of martial arts such as tai chi, relaxation disciplines such as yoga, or general exercise, seem to mitigate fatigue and improve quality of life.

Prognosis

The prognosis (the expected future course of the disease) for a person with multiple sclerosis depends on the subtype of the disease; the individual's sex, race, age, and initial symptoms; and the degree of disability the person experiences. The life expectancy of people with MS, at least for earlier years, is now nearly the same as that of unaffected people. This is due mainly to improved methods of limiting disability, such as physical therapy, occupational therapy and speech therapy, along with more successful treatment of common complications of disability, such as pneumonia and urinary tract infections. Nevertheless, half of the deaths in people with MS are directly related to the consequences of the disease, while 15% more are due to suicide.

- Individuals with progressive subtypes of MS, particularly the primary progressive subtype, have a more rapid decline in function. In the primary progressive subtype, supportive equipment (such as a wheelchair or standing frame) is often needed after six to seven years. However, when the initial disease course is the relapsing-remitting subtype, the average time until such equipment is needed is twenty years. This means that many individuals with MS will never need a wheelchair. There is also more cognitive impairment in the progressive forms than in the relapsing-remitting course.

- The earlier in life MS occurs, the slower disability progresses. Individuals who are older than fifty when diagnosed are more likely to experience a chronic progressive course, with more rapid progression of disability. Those diagnosed before age 35 have the best prognosis. Females generally have a better prognosis than males. Although individuals of African descent tend to develop MS less frequently, they are often older at the time of onset and may have a worse prognosis.

- Initial MS symptoms of visual loss or sensory problems, such as numbness or tingling, are markers for a relatively good prognosis, whereas difficulty walking and weakness are markers for a relatively poor prognosis. Better outcomes are also associated with the presence of only a single symptom at onset, the rapid

development of initial symptoms, and the rapid regression of initial symptoms.

- The degree of disability varies among individuals with MS. In general, one of three individuals will still be able to work after 15–20 years. Fifteen percent of people diagnosed with MS never have a second relapse, and these people have minimal or no disability after ten years. The degree of disability after five years correlates well with the degree of disability after fifteen years. This means that two-thirds of people with MS with low disability after five years will not get much worse during the next ten years. It should be noted that most of these outcomes were observed before the use of medications such as interferon, which can delay disease progression for several years.

- Apart from physical disability, cognitive impairment in MS occurs in approximately half of all patients. In its earlier stages, this impairment can include loss of short-term memory, depression and the pseudobulbar affect. As the disease progresess, the impairment can become more profound, ranging from loss of deductive reasoning to dementia.

Currently there are no clinically established laboratory investigations available that can predict prognosis or response to treatment. However, several promising approaches have been proposed. These include measurement of the two antibodies anti-myelin oligodendrocyte glycoprotein and anti-myelin basic protein, and measurement of TRAIL (TNF-related apoptosis-inducing ligand).