

Multiple sclerosis: An overview

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Abstract

The multiple sclerosis, involves the degeneration of neurones, leading to slowing in conduction of impulses as well as leading scars. A number of causative factors have been suggested for MS, yet the exact aetiology is unknown. The diagnosis as well as treatment methods including steroidal moieties are being used in common practice, yet a specific diagnosis procedure is required. Beside these the overcome from the adverse reactions of steroids are also required. Aim of present article is to summarise the various aspects of multiple sclerosis.

Keywords: multiple sclerosis, scar, steroid, Immune system

1. Introduction

Multiple sclerosis signifies both the number (multiple) and condition (sclerosis) of the demyelinated areas in the central nervous system¹. During an MS attack, inflammation occurs in white matter of central nervous system in random patches i.e plaques. This process is followed by destruction of myelin, the fatty covering that insulates nerve cell fibres in the brain and spinal cord. Myelin facilitates smooth, high-speed transmission of electrochemical messages between the brain, spinal cord and rest of the body; when it is damaged, neurological transmission of messages may be slowed or blocked completely, leading to diminished or lost function. Multiple Sclerosis [MS], is widely considered to be an autoimmune chronic disease, in which neuronal protective membrane get damaged by their own immune system and this causes a lack of protection for the central nervous system and a loss in the ability to properly transmit nerve signals, resulting in diminished neuronal impulse conduction². Initially; the symptoms appeared are reversible, consequently altering the vision, speech, walking, writing, and memory. It is often difficult for a specialist to properly predict what path the MS may take in separate patients. It is not contagious and therefore cannot be transmitted from one person to another. MS is also not an inherited disease, in the direct sense but some research has suggested that a disposition to developing the problem can exist in certain genes. One theory for this disease is related with deficiency of oligodendrocytes, an essential factors for the synthesis of axonal material, such as insulin-like growth Factor-1 (IGF-1), brain derived neurotrophic factor (BDNF) etc. All these processes, inflammation, demyelination, oligodendrocyte death, membrane damage and axonal death contribute to the symptoms of MS³.

2. Factors causing Multiple sclerosis

The various agents resulting as MS are following:

2.1 Immune System: Immune system is responsible to protect body from foreign matters. The researches suggest that during multiple sclerosis, a foreign agent such as a virus alters the immune system; so that the immune system perceives myelin as an intruder and attacks it⁴. During this disease malfunctioning of immune system of patients is observed involving altered profile of T cells. With multiple sclerosis, myelin is removed from brain, the spinal cord and the optic nerves are replaced by internal scars which are called 'sclerotic tissue'. It is the lack of myelin which causes the symptoms of MS. When any part of this myelin sheathing is destroyed, nerve impulses to the brain are interrupted and distorted⁵.

The myelin components like myelin basic protein on administration in animals precipitate experimental allergic encephalomyelitis (EAE), a chronic relapsing brain and spinal cord disease that resemble MS. The injected myelin probably stimulates the immune system to produce anti-myelin T cells that attack the animal's own myelin.

2.2 Destruction of blood-brain barrier: The blood brain barrier, a protective membrane that controls passage of substances between blood and CNS may get disoriented, leading MS symptoms^{6,7}.

2.3 Environmental factors: Different environmental factors, both of infectious and non infectious origin may be risk factor for MS. MS is more common in people who live farther from the equator, although many exceptions exist. Decreased sunlight exposure i.e. vitamin D production and intake, may precipitate the MS. It is five times more prevalent in temperate climates-such as those found in the northern United States, Canada, and Europe-than in tropical regions. Furthermore, the age of 15 seems to be significant in terms of risk for developing the disease. Some studies indicate that a

person moving from a high-risk (temperate) to a low-risk (tropical) area before the age of 15 tends to adopt the risk of the new area and vice versa. Other studies suggest that people moving after age 15 maintain the risk of the area where they grew up.

These findings indicate a strong role for an environmental factor in the cause of MS. It is possible that, at the time of or immediately following puberty, patients acquire an infection with a long latency period. Or, conversely, people in some areas may come in contact with an unknown protective agent during the time before puberty. Other studies suggest that the unknown geographic or climatic element may actually be simply a matter of genetic predilection and reflect racial and ethnic susceptibility factors.

2.4 Genetics: However researches revealed that the genetical predisposition of MS is very less, yet it has been documented by some authors. They have drawn attention on human leukocyte antigen (HLA) or major histocompatibility complex region on chromosome 6.^{8, 9} Studies 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 MS¹⁰⁻¹³. These studies strengthen the theory that MS is the result of a number of factors rather than a single gene or other agent.

2.5 Microbial Infection: Many microbes have been proposed as potential infectious triggers of MS, but none have been substantiated. Viral infections are usually accompanied by inflammation and the production of gamma interferon, a naturally occurring body chemical that has been shown to worsen the clinical course of MS. It is possible that the immune response to viral infections may themselves precipitate an MS attack. There seems to be little doubt that something in the environment is involved in triggering MS. Evidence for viruses as a cause includes the presence of oligoclonal bands in the brain and cerebrospinal fluid of most patients, the association of several viruses with human demyelination encephalomyelitis, and induction of demyelination in animals through viral infection. Individuals who have never been infected by the Epstein-Barr virus have a reduced risk of having the disease, and those infected as young adults have a greater risk than those who had it at a younger age.

Severe stress, smoking, association with occupational exposures and toxins, diet and hormone intake have also been denoted as a cause of MS¹⁴.

3. Types of MS

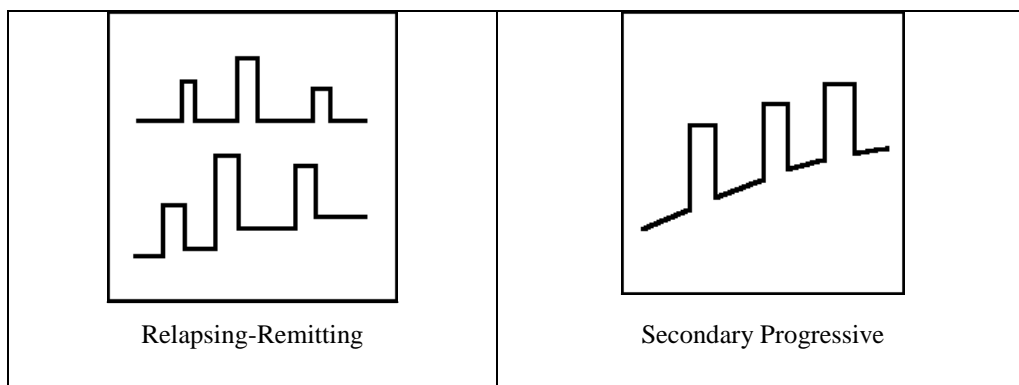
There are different clinical manifestations of multiple sclerosis. During an attack, a person experiences a sudden deterioration in normal physical abilities that may range from mild to severe. This attack sometimes referred as an exacerbation of multiple sclerosis, typically lasts more than 24 hours and generally more than a few weeks¹⁵. 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. They are important not only for prognosis but also for therapeutic decisions. In 1996 the United States National Multiple Sclerosis Society standardized four subtype definitions.

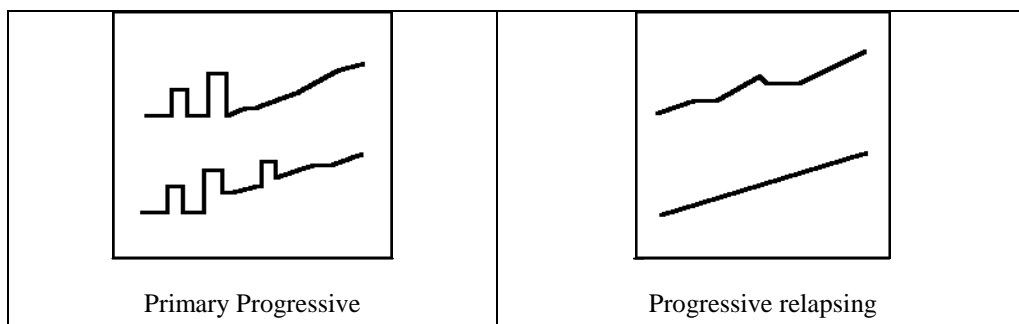
3.1 Relapsing Remitting (RR-MS): it is characterized by unpredictable relapses followed by periods of months to years of relative quiet (remission) with no new signs of disease activity. In this form of MS there are unpredictable relapses occur, during which new symptoms appear or existing symptoms become more severe.

3.2 Secondary Progressive (SP-MS): Those beginning with RR-MS can then enter a phase where relapses are rare but more disability accumulates, and are said to have secondary-progressive (SP) MS. In this condition a steady decline in abilities accompanied by sporadic attacks

3.3 Primary Progressive (PP-MS): This form of MS is characterised by a lack of distinct attacks, but with slower onset and steadily worsening symptoms. There is an accumulation of deficits and disability which may level off at some point or continue over months and years. It is characterized by progression of disability from onset, with no, or only occasional and minor, remissions and improvements.

3.4 Progressive Relapsing (PR-MS): Describes those individuals who, from onset, have a steady neurologic decline but also suffer clear superimposed attacks. This is the least common of all subtypes





4. Effect of Life Events on the Course of MS

Studies have shown that MS has no adverse effects on the course of pregnancy, labour, or delivery; in fact symptoms often stabilize or remit during pregnancy. This temporary improvement is thought to relate to changes in a woman's immune system that allow her body to carry a baby. Because every foetus has genetic material from the father as well as the mother, the mother's body should identify the growing foetus as foreign tissue and try to reject it in much the same way the body seeks to reject a transplanted organ. To prevent this from happening, a natural process takes place to suppress the mother's immune system in the uterus during pregnancy¹⁶.

5. Symptoms of Multiple Sclerosis (MS)

The early symptoms of multiple sclerosis can vary greatly, characteristically, the symptoms tend to repeated, anywhere from eye sight problems to slurred speech. Over time some people may develop paralysis or severe motor disabilities, while in others the symptoms may go away completely^{17,18}.

Symptoms of MS may be mild or severe, of long duration or short, and may appear in various combinations, depending on the area of the nervous system affected. Complete or partial remission of symptoms, especially in the early stages of the disease, occurs in approximately 70 percent of MS patients. The initial symptom of MS is often blurred or double vision, red-green colour distortion, or even blindness in one eye. Inexplicably, visual problems tend to clear up in the later stages of MS. Inflammatory problems of the optic nerve may be diagnosed as retrobulbar or optic neuritis. Most MS patients experience muscle weakness in their extremities and difficulty with coordination and balance at some time during the course of the disease. These symptoms may be severe enough to impair walking or even standing. In the worst cases, MS can produce partial or complete paralysis. Most people with MS also exhibit paresthesias, transitory abnormal sensory feelings such as numbness, prickling, or "pins and needles" sensations; uncommonly, some may also experience pain. Loss of sensation sometimes occurs. Speech impediments, tremors, and dizziness are other frequent complaints. Occasionally, people with MS have hearing loss. Approximately half of all people with MS experience cognitive impairments such as difficulties with concentration, attention, memory, and poor judgment, but such symptoms are usually mild and are frequently overlooked. In fact, they are often detectable only through comprehensive testing. Cognitive symptoms occur when lesions develop in brain areas responsible for information processing. Types of memory problems may differ depending on the individual's disease course (relapsing-remitting, primary-progressive, etc.), but there does not appear to be any direct correlation between duration of illness and severity of cognitive dysfunction. Depression, which is unrelated to cognitive problems, is another common feature of MS. Actual emotional state-known as laughing/weeping syndrome, is thought to be due to demyelisation in the brainstem, the area of the brain that controls facial expression and emotions, and is usually seen only in severe cases. In about 60 percent of MS patients, heat-whether generated by temperatures outside the body or by exercise-may cause temporary worsening of many MS symptoms. In these cases, eradicating the heat eliminates the problem. Some temperature-sensitive patients find that a cold bath may temporarily relieve their symptoms.

6. Diagnosis of MS

Most people who have multiple sclerosis can expect to live to a normal, or nearly normal, age. Only a minority of sufferers actually develop any serious disability as a result of having the disease. Typically; multiple sclerosis is first diagnosed in people between the ages of twenty and forty five, although there have been cases of very young children and very old people also developing the disorder¹⁹.

A physician can diagnose MS in some patients soon after the onset of the illness. In others, however, physicians may not be able to readily identify the cause of the symptoms, leading to years of uncertainty and multiple diagnoses punctuated by baffling symptoms that mysteriously wax and wane. Some of the diagnosis approaches for MS are as;

Biomarkers: Currently there are no clinically established laboratory investigations available that can predict prognosis. However, several promising approaches have been proposed. Investigations on the prediction of evolution have centred on monitoring disease activity. Disease activation biomarkers include interleukin-6, nitric oxide and nitric oxide synthase, osteopontin, and fetuin-A. On the other hand since disease progression is the result of neuro degeneration the roles of proteins indicative of neuronal, axonal, and glial loss such as neurofilaments, tau and N-acetylaspartate are under

investigation. A final investigative field is work with biomarkers that distinguish between medication responders and non responders.

MRI (magnetic resonance imaging) scans, with intravenous gadolinium helps to identify, describe lesions in the brain (plaques)²⁰. At the same time, electro-physiological test including CSF examination helps in diagnosis of MS²¹.

7. Treatments

The primary goal of the treatment of MS is to avoid recurrence of attacks (usually with steroid drugs), reducing the number of attacks or the number of MRI lesions; or attempting to slow progression of the disease (treatment with disease modifying drugs or DMDs).

Drugs known to affect the immune system have become the primary focus for managing multiple sclerosis. Initially, corticosteroids, such as prednisone or methylprednisolone were widely used. However, since their effect on the immune system is non-specific (general) and they may cause numerous side effects, corticosteroids now tend to be used to manage only severe multiple sclerosis attacks (attacks leading to physical disability or causing pain)²².

Complications associated with MS are managing with drugs like, slowness (dalfamipridine), muscle spasticity (baclofen, tizanidine etc), acute optic neuritis (methylprednisolone), Fatigue, and emotional outbursts (Anti-depressants), Pain (NSAID,S), Bladder dysfunction (Antibiotics and Vit C) etc.

7.1 MS treatments: with Steroids: Steroids work by decreasing the levels of the 'bad' immune chemicals and by making the cell membranes of the white cells more pliable and less sticky.

Steroids are naturally occurring hormones in human body. Corticosteroids are synthetic replications of natural hormones produced in adrenal glands. They seem to have an anti-inflammatory function and were some of the first drugs used to combat MS attacks. There are a variety of steroids including glucocorticosteroids, mineralcorticosteroids, androgens and progestin. Of these, only the glucocorticosteroids (often simply called glucocorticoids) are regularly prescribed to treat relapses in multiple sclerosis^{23, 24}.

Cortisone and hydrocortisone are natural glucocorticosteroids. The cortisones are produced from adrenal cortex in response to the release of a regulatory hormone i.e. adrenocorticotrophic hormone (ACTH) of pituitary gland. Cortisones have an immunosuppressive effect by deactivating white blood cells specifically T-cells by inhibiting their release of messenger molecules called cytokines and effector molecules. This form of immune-regulation is known as lymphocytopenia. Although they can be effective in hastening recovery from a relapse they do not in any way 'fix' the problem and prevent further episodes of MS from occurring.

During an MS relapse there is a breaking down of the 'blood brain barrier' (BBB), so that harmful substances from the bloodstream can cross this barrier and reach the brain and spinal cord. The steroids are thought to help stabilise the BBB and help in close up this leaking. They also reduces inflammation of CNS, so allowing brain signals to be transmitted for 'normal' body function again. However with autoimmune diseases the immune system goes starts attacking its own organs or tissue, and in case of MS this is the myelin sheath of nerves cell, while corticosteroids can help by decreasing the harmful autoimmune activity.

During an infusion some people experience a metallic taste in their mouth. Other short-term side effects can include increased heart rate, hot flushes, a red face, sleeping problems, mood swings or even a sense of euphoria. Cortisones also induce a degree of white blood cell death and is also believed that they reduce the "leakiness" of the blood-brain barrier.

7.2 Interferons for relapsing multiple sclerosis: Interferons are protein messengers that cells of the immune system manufacture and use to communicate with one another. There are different types of interferons, such as alpha, beta, and gamma. All interferons have the ability to regulate the immune system and play an important role in protecting against intruders including viruses. Each interferon functions differently, but the functions overlap. The beta interferons have been found useful in managing multiple sclerosis. Interferons are thought to decrease the ability of immune cells to interact with other cells, to penetrate the blood brain barrier, and to produce the swelling and inflammation that is associated with demyelination.

8. Conclusions

The side effects that may occur with prolonged corticosteroid use can be a problem for people who have frequent MS attacks and need repeated treatment with corticosteroids. Although a number of approaches have been made to treat the MS conditions, yet more work is required to eliminate the condition from the society. At the same time newer and fast diagnostic techniques are also to be incorporated in clinical practices.

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