MULTIPLE SCLEROSIS: A REVIEW

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ABSTRACT

Multiple sclerosis affects around 2.5 million people worldwide it is one of the most common neurological disorders and cause of disability of young adults, especially in Europe and North America. There is a lack of epidemiological studies from Asia where the prevalence is reported to be low, though, with the availability of more neurologists and magnetic resonance imaging, a larger number of patients are being diagnosed. MS is a slowly progressive, immunologically mediated disease of the central nervous system, characterized by inflammation and demyelination of white matter in the brain and spinal cord. A triad of symptoms clinically characterize Multiple sclerosis: changes in sensation, muscle weakness, ataxia, dysarthria, dysphagia, visual problems, fatigue, acute or chronic pain, bladder and bowel difficulties. The diagnosis of MS is made on the basis of the clinical signs and symptoms, with magnetic resonance imaging (MRI) and other laboratory tests playing a supportive role. All tests are non specific and only provide supportive evidence for diagnosis. The effective management of multiple sclerosis is complex and draws on many disciplines, such as neurologists, physiotherapists, speech therapists, counsellors, general practitioners, nurses and pharmacists. There has been no specific treatment for multiple sclerosis so far. The therapies used to treat MS are targeted at different aspects of the disease and can be categorized into disease modifying therapies, treatments used in acute exacerbations and drugs used to treat disease complications.

INTRODUCTION:

Multiple sclerosis affects around 2.5 million people worldwide it is one of the most common neurological disorders and cause of disability of young adults, especially in Europe and North America. There is a lack of epidemiological studies from Asia where the prevalence is reported to be low, though, with the availability of more neurologists and magnetic resonance imaging, a larger number of patients are being diagnosed. Although some people experience little disability during lifetime, up to 60% are no longer fully ambulatory 20 years after onset, with significant implications for their quality of life and the finical cost to society[1]. Disease onset usually occurs in young adults, and it is more common in females[2]. The prevalence of MS is 1 per 1000 people and the ratio of female to male patients is 1.5 to 1. MS has heterogeneous clinical presentations and courses, ranging from benign to classical relapsing remitting (RR; prevalence 45 %), primary progressive (PP; prevalence 20 %) and secondary progressive (SP; prevalence 45 %) or rare fulminant disease courses[3]. MS was first described in 1868 by Jean-Martin Charcot [4]. Multiple sclerosis (MS) is an inflammatory demyelinating condition of central nervous system (CNS) that is generally considered to be autoimmune in nature. In people with MS, the immune trigger is unknown, but the targets are myelinated CNS tracts. In regions of inflammation, break-down of blood-brain barrier occurs and destruction of myelin ensues, with axonal damage, gliosis and formation of sclerotic plaques [1]. MS is a slowly progressive, immunologically mediated disease of the central nervous system, characterized by inflammation and demyelination of white matter in the brain and spinal cord. The myelin sheath influences the rate of nerve impulse conduction with transmission being more rapid in myelinated nerve fibres. In MS the sheaths deteriorate to scleroses, which are hardened scars or plaques in multiple regions [5]. In MS, an autoimmune response is evoked that causes the body to attack its own myelin[6]. The disease is usually characterised by a relapsing remitting course in the early stages, with full or nearly full recovery initially. In the early stages there may be little damage to axons. Over time the disease enters an irreversible progressive phase of neurological deficit [7]. Acute relapses are caused by inflammatory demyelination [8], while disease progression is thought to result from axonal loss[9]. Each relapse causes further loss of nervous tissue and progressive dysfunction. In some cases there may be chronic progression without remission or acute disease rapidly leading to death[9]. There is no known cure for MS. Treatments attempt to return function after an attack, prevent new attacks, and prevent disability. The prognosis is difficult to predict; it 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.

Clinical Signs and Symptoms

The clinical signs and symptoms of multiple sclerosis depend on where the plaques are formed and differ greatly between patients. A triad of symptoms clinically characterize Multiple sclerosis: changes in sensation (hypoesthesia and paraesthesia), muscle weakness, 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, acute or chronic pain, bladder and bowel difficulties[2,10].Multiple sclerosis relapses are often unpredictable, occurring without warning and without obvious inciting factors with a rate rarely above[1] and a half per year [2]. Some attacks, however, are preceded by common triggers.

Relapses occur more frequently during spring and summer. Viral infections such as the common cold, influenza, or gastroenteritis increase the risk of relapse[2].

Diagnosis of MS

The diagnosis of MS is made on the basis of the clinical signs and symptoms, with magnetic resonance imaging (MRI) and other laboratory tests playing a supportive role. All tests are non specific and only provide supportive evidence for diagnosis.

Laboratory tests in MS:

Magnetic resonance imaging (MRI)

MRI is the single most useful laboratory test in the diagnosis of MS. In 1981, Young et al have com- pared MRI and CT scans in patients with MS. They demonstrated that MRI not only picked up all the lesions seen on the CT scan, it revealed many more, particularly in the brain stem. The lesions also had more distinct margins. All patients had multiple lesions on MRI and many of these were per ventricular and hence considered specific for MS by these authors [11,12]. In 1988, Isaac et al have demonstrated that MRI evidence for disease activity is much more frequent than clinical evidence [13].

Electrophysiological tests

i. Visual evoked potentials (VEP) are most frequently employed in clinical practice. Since MS affects anterior optic pathways, VEP reveal abnormality in significant number of patients. In the series of Halliday *et al* 86% patients of MS who had no history of ON and had normal optic disc showed an abnormal VEP[14].

ii. Brainstem auditory evoked potentials (BAEP) have also been used in the diagnosis of MS. Sixty percent of patients without clinical signs of brainstem involvement showed abnormalities. of BAEP [15].

3. Other laboratory tests

i. The examination of cerebrospinal fluid (CSF)

has been used to support the diagnosis of MS for a long time. The presence of myelin basic protein in the CSF of MS patient may be highly suggestive of activity of MS process but its absence does not rule out active disease[16].

ii. Presence of IgG oligoclonal band in the CSF has proved to be the most sensitive laboratory test in the diagnosis of MS and is not dependent on the activity of the disease and treatment received by the patient.

Classification of Multiple Sclerosis:

MS is essentially divided into four main courses:

1-Relapsing-remitting MS:- Episodes of acute worsening of neurologic function, with some amount of recovery (the most common form) and no progression in between [2]. Approximately 80% of patients will initially present this form of MS, in which there are unpredictable attacks (relapses) during which new symptoms appear or existing symptoms become more severe. The relapses can last for varying period (day or month) and there is partial or total recovery / remission[1, 17].

Primary-progressive MS:- Continuing worsening of disease without distinct relapses[1]. This affects around 10-15% of all MS patients, is characterized by a lack of distinct attacks, but with slow onset and then stedily worsening symptoms? There is an accumulation of deficits and disability which may level off at some point or continue over years [1, 18].

Secondary-progressive MS:- Relapsing-remitting disease initially, eventually converting to a progressive form with a gradual loss of function. It is characterized by

progression that is not relapse related [2]. Approximately 50 % of patients with relapsing/ remitting MS will develop secondary progressive MS within 10 years, and 80 % will have developed this form of MS within 20 years of disease onset [1, 19].

Progressive-relapsing: - Progressive disease from onset, with acute relapses and continuing disease progression [1, 2].

Pathophysiological Features of Multiple Sclerosis:

The pathological signature of MS is the white matter plaque, a circumscribed area of demyelination and relative axonal preservation. Plaques may occur anywhere within the white matter but favour the periventricular regions, optic nerves, brain stem, cerebellum, and spinal cord. Depending on their stage of development, they contain varying proportions of immune cells and immune reactive substances.

Multiple sclerosis (MS) is a disease in which the fatty myelin sheaths around the axons of the brain and spinal cord are damaged, leading to demyelination and scarring as well as a broad spectrum of signs and symptoms [2, 20]. MS affects the ability of nerve cells in the brain and spinal cord to communicate with each other. Nerve cells communicate by sending electrical signals called action potentials down long fibers called axons, which are wrapped in an insulating substance called myelin. In MS, the body's own immune system attacks and damages the myelin. When myelin is lost, the axons can no longer effectively conduct signals. The name *multiple sclerosis* refers to scars (scleroses—better known as plaques or lesions) in the white matter of the brain and spinal cord, which is mainly composed of myelin [20]. Although much is known about the mechanisms involved in the disease process, the cause remains unknown. Theories include genetics or infections. Different environmental risk factors have also been found [21].

Immune Dysfunction and Damage to CNS:-MS is characterized by the formation of multiple lesions along the nerve fibers in the brain and spinal cord. The key players include:

1- Axons, the nerve fibers that transmit information via electrical signals
2- Myelin, the fatty substance that wraps around the axons like an insulating sheath. Oligodendrocytes, the cells that make up the myelin
3- Blood vessels that supply oxygen and nutrients
4- Inflammatory factors, such as cytokines.
5- T-cells, a form of white blood cell presenting cells, which introduce the myelin antigen to the T cell

MS is thought to be an autoimmune disease, but what triggers the immune system to attack the body is still unclear. During this immune response, cells that identify antigens are somehow triggered to interpret one of the components of myelin as foreign. When antigen presenting cells introduce the myelin antigen to the T cells, the T cells pass through the blood–brain barrier and mount an attack on the myelin, activating more T cells and other immune cells in the process [22]. Other inflammatory factors, such as cytokines, are released, and the end result is an immunologic cascade that produces tissue damage, not only to the myelin sheath, but to the underlying axons as well. This "demyelination" makes the transmission of information via axons more difficult ultimately, there is interference with the conduction of nerve impulses from the sensory organs to the CNS and from the CNS to the muscles. Injury to the axons themselves, called "axonal damage," can be part of this destructive process even early in the disease

and may result in permanent loss of neuronal transmission[23]. At least initially, however, the process of MS is typically a waxing and waning one. Inflammatory episodes occur in the form of periodic acute attacks, and once the inflammation subsides [24], impaired function is usually recovered either completely or partially. Reversal of inflammation or the process of "remyelination" can occur over and over, or, permanent damage may occur at any time [25].

Possible Triggers: - While MS is almost certainly an autoimmune disease, the factor or factors that trigger an attack on the spinal cord and brain's white matter remain unknown. A number of hypotheses are being explored, one being the role of viruses. Peripheral blood antibody titers too many viruses are elevated in people with MS. These include varicella zoster, vaccinia, rubella, Epstein–Barr, human herpes virus 6 (HHV-6), and others. In some cases, virus-specific antibody is also detected in the cerebrospinal fluid, and recently some viruses, especially HHV-6, have been detected near the characteristic brain lesions of some persons with MS. The relevance of these findings to the pathophysiology of the disease remains to be determined[26]. Its causes and the factors that contribute to its heterogeneity are largely unknown, although it is likely a complex trait with genetic and environmental components. The disease affects about 0.1% of the population in temperate climates, some 250,000 to 350,000 people in the United States. It is a disease of young people (median age of onset is approximately 28 years) but is lifelong and is often disabling; 50% of patients require a cane to walk 15 years after disease onset [3]

Environment and Genetics: - The cause of MS is not known. Epidemiological findings support both environmental and genetic hypotheses, and these forces likely interact to produce individual disease susceptibility and influence disease course. Several observations seemingly support environmental hypotheses. The prevalence of MS generally increases with distance from the equator, and apparent epidemics and clusters of MS have been reported. Migration (and age at migration) may modify the disease risk, and concordance rates in monozygotic twins do not exceed approximately 30%[27]. Some consider these findings as supportive of an ecological or infectious hypothesis for MS susceptibility. It is unclear whether putative environmental factors are operative at the individual level (e.g., infectious, transmissible agents) or elevate the risk of the entire population (e.g., ecological factors, such as climate, soil conditions, or diet) [28].Ecological case-control studies are often limited because exposures are usually similar amongst cases and controls. Isolation of infectious agents and/or serological evidence of greater exposure in MS cases compared to controls have been reported frequently over several decades. Recent reports implicate human herpes virus 6 (HHV-6) [20, 29] and *Chlamydia pneumoniae* [30] as causative agents, but others have failed to confirm these observations [31]. To date, no single infectious agent has withstood the test of time. Genetic predisposition to MS has been established from the following evidence: familial aggregation unexplained by environmental factors[32]; much higher monozygotic than dizygotic twin concordance rate (31% versus 5%)[33]; ethnic predisposition (eg, Northern Europeans) and protection (many groups, including North American Indians and Hutterites, despite living in regions with high MS prevalence); and association with human leukocyte antigen (HLA) DR2. The exact mode of inheritance is unknown but does not appear to be Mendelian or mitochondrial in nature. In general, the risk to a first-degree relative is approximately 1% to 4% (10–40 times the population risk), but this

value may be substantially higher in pedigrees with multiple affected members.

The genes that contribute to MS susceptibility have not been identified. The HLA DR2 allele has been associated with MS in many populations [32]. Four entire human genome screens by linkage have been reported[34,35]. Although refinement of the original genome screens continues[36], the most consistent evidence of a susceptibility locus appears to be the HLA region on chromosome 6. It seems unlikely that any other single genes contribute a significant risk. Genetic factors may also determine disease course and severity, but HLA polymorphisms are not significant contributors[37]. Polymorphisms in the interleukin-1b-receptor and interleukin-1b-receptor antagonist genes[38], the apolipoprotein E gene[39], and immunoglobulin Fc receptor genes [40] have been associated with disease course. These associations require confirmation.

Therapeutic management

The effective management of multiple sclerosis is complex and draws on many disciplines, such as neurologists and allied health workers like physiotherapists, occupational and speech therapists, counsellors and social workers as well as consultants, general practitioners, nurses and pharmacists. There has been no specific treatment for multiple sclerosis so far. The therapies used to treat MS are targeted at different aspects of the disease and can be categorized into disease modifying therapies, treatments used in acute exacerbations and drugs used to treat disease complications.

Disease modifying therapies: - The most plausible theory concerning the cause of MS is that it is an abnormal, autoimmune response. Therefore, most drugs in this category set out to modify the immune system, either by stimulation or suppression.

1. **Interferon-** The interferon are naturally occurring amino acids and are cytokines. They are synthesised in response to viruses and act on other cells to prevent them becoming infected. Gamma interferon produced by T cells is thought to activate macrophages which then destroy myelin directly and has been shown to exacerbate MS. Interferon alpha and beta are produced by many different cells, including macrophages, fibroblasts and endothelial cells. Interferon beta is known to have immune-modulatory effects[41].

These include inhibition of leukocyte proliferation and antigen presentation, inhibition of T-cells migration across the blood brain barrier and modulation of cytokine production to produce anti-inflammatory environment[42] of the beta interferon's, 1a and 1b (IFNB-1a and IFNB-1b) have been shown to be most beneficial in multiple sclerosis. IFNB-1a and IFNB -1b are similar in their biological activity and in vivo pharmacokinetics[43]. There are three preparations in use, Avonex, Rebif (interferon beta-1a) and Betaferon (interferon beta-1b). Avonex is given by intramuscular injection at a dose of 30 μg (6 million IU) once a week. Rebif is given subcutaneously at a dose of 22 μg (6 million IU) three times a week. Betaferon is given subcutaneously at a dose of 0.25 mg (8 million IU) on alternate days. The most common adverse effect is a flu-like syndrome, which is prominent at the start of therapy and then wear off with continued treatment. NSAIDs are recommended prophylactically before each interferon dose to alleviate the symptoms.

2. **Glatiramer acetate (copolymer-1)** It is a synthetic polypetide analogue of myelin basic protein. It was accidentally discovered during attempts to induce experimental allergic encephalomyelitis in animals (the animal model of MS). Its mode of action has not been defined, although it is thought to involve inhibition of lymphocyte migration (44) and suppression of T-cell activation [45]. It may exert its effect by competing with myelin basic protein and perhaps other myelin auto antigens for binding to MHC Class II molecules expressed on antigen presenting cells [46]. It is given daily at a dose of 20 mg subcutaneously and is well tolerated with the most common adverse experience being injection site reaction. A two year study demonstrated a 29% reduction in relapse rate in patients with RRMS [47, 48].

3. **Intravenous immunoglobulin (IgG)** In a two-year randomised controlled trial, approximately 150 patients with RRMS showed a favourable effect on relapse rate in the treatment group who received intravenous immunoglobulin[49].

4. **Cytotoxic   immuno-suppressants** Immunosuppressant drugs such as cyclophosphamide,   mofetil, mitozantrone[50],   azathioprine[51]   and cyclosporin offer only modest benefits and in general, these benefits are outweighed by their side Effects [52,53].

5. **Low-dose methotrexate-** Once weekly treatment of methotrexate at a low dose (7.5 mg) has been shown to slow significantly the progression of chronic progressive MS[54].

6. **Cladribine   Cladribine   (2-chlorodeoxyadenosine)** is a purine antimetabolite and its use in MS is controversial. Side effects included thrombocytopenia, bone marrow suppression and herpes zoster attacks[55-56].

7. **Linomide-** Linomide (quinoline-3-carboxamide) is a synthetic immunomodulator that acts by stimulating killer T cells. It also interferes with antigen presentation (57). Linomide (2-5 mg daily by mouth) has been shown to suppress disease activity in those with SPMS (58). However, phase III trials were prematurely stopped due to a higher than expected incidence of myocardial infarction in the linomide-treated group[59].

8. **Anti- α 4 integrin (Antegren)-** Antegren is a monoclonal antibody directed against 4 integrin, a cell adhesion molecule involved in immune cell migration. A trial of 72 patients with active RRMS or SPMS reported a significant reduction in the number of active lesions on MRI after short term treatment with intravenous antegren [60, 61]. Further studies are underway.

Treatments used in acute exacerbations

Acute exacerbation in the neurological status of a patient with multiple sclerosis may be due to an episode of inflammatory demyelination (relapse). Inter-current infection (especially urinary tract infection), electrolyte imbalance, fever or drug intoxication. In a relapse, neurological deterioration normally occurs over several days and recovery takes weeks to months. Corticosteroids are useful in accelerating recovery from an acute exacerbation, but do not affect long - term disability[62]. Corticosteroids are now normally used in treating relapses and are thought to act by reducing oedema and inflammation and consequently resolving conduction block. They

help to speed the rate of recovery but do not affect the eventual degree of recovery[63]. No conclusion has been reached as to which steroid is definitely superior [64-66]. The most popular choice is intravenous methyl prednisolone[67].

The beneficial action of corticosteroids in MS is probably two-fold, involving both their immunosuppressive and anti-inflammatory effects. In MS, corticosteroids reduce inflammation and oedema around the plaques, which lowers the pressure on the axons and allows better nerve impulse conduction. Corticosteroids also repair the damaged BBB by reducing inflammation and hence reducing the passage of white blood cells and other inflammatory mediators through to the CNS. Immunosuppressant action of corticosteroids may exacerbate the infection, which in some cases, may lead to septicaemia. Side effects include restlessness, anxiety and insomnia. Depression psychosis or euphoria may also arise.

Oral steroids: - Oral prednisolone may be effective in shortening acute attacks of MS and tends to be used in the community in preference to intravenous steroids when relapses are not severe[68, 69].

Plasma exchange: - Therapeutic plasma exchange has been shown to benefit patients with severe relapses that have not responded to intravenous corticosteroids [70].

Involvement of blood brain barrier in MS: - The BBB is a feature of the blood capillaries found in the CNS. Historically, it has been known that MS is caused by certain white blood cells attacking the myelin surrounding the nerve cells of a person's own central nervous system[71]. Under normal condition BBB provides an effective separation between the blood cells and the myelin, such that the white blood cells should not have access in order to attack the myelin surrounding the nerve cells.

White blood cells also release matrix metallo-proteinases (MMPs) which are activated by exposure to other enzymes [71] weakening the intercellular cement.

There is another process which also has the potential to attack BBB integrity when white blood cells destroy invading organisms, superoxide and free radicals are released which are extremely active and can destroy many of the tissues they contact. However, when the process takes place at the BBB, it can be one more attack on the integrity of the barrier. A simple potential treatment for multiple sclerosis will be the strengthening of the BBB to the extent that no further breakdowns occur. Anthocyanosides, proanthocyanidins and procyanidolic oligomers have been found effective in strengthening the BBB in animals [72].

Neurorehabilitation: - The Philosophy of Neurorehabilitation, which emphasizes patient education and self –management, is well suited to meet the complex and variable needs of MS [73]. Neurologists will be the main physicians involved, but depending on the symptom, doctors of other medical specialties may also be helpful. Allied treatments such as physiotherapy[72], speech and language therapy[74] or occupational therapy[75] can also help to manage some symptoms and maintain quality of life.

Multidisciplinary approaches have been shown to be effective in increasing activity levels and participation in multiple sclerosis[76]. Due to the paucity of randomized controlled studies, there is limited evidence of the overall efficacy of individual therapy disciplines, though there is good evidence that specific approaches, such as exercise [77],psychology therapies, particularly cognitive behavioural approaches and energy conservation instruction are effective [78].

Concluding Remarks:

Multiple sclerosis (MS) is the most important human inflammatory demyelinating disease characterized by recurrent neurological relapses and/or progression that occur from multifocal white matter and cortical lesions within the central nervous system (CNS). MS is a chronic, progressive and essentially incurable disease that most often affects young adults. It is thought to be an autoimmune disease that affects the central nervous system. The course of MS is unpredictable and variable on a day-to-day and an individual patient basis. As chronic problems accumulate, the disease may become more steadily progressive, with fewer or no acute relapses.

A diagnosis of MS is a clinical one based on a thorough history and neurologic examination, and supported by MRI and other diagnostic tests. Management strategies fall into three general categories: acute treatment of relapses, prevention of progression or reduction in the frequency of relapses. The search for new drug treatment for MS is gaining momentum and the future looks brighter, although a cure for MS is still some way off.

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