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Review: Multiple Sclerosis and its Pathophysiology: A Narrative Review

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ABSTRACT

Multiple sclerosis (MS) is one of the most important debilitating diseases in which the myelin sheaths of nerve cells in the brain and spinal cord are damaged. In this review, we aimed to review the pathophysiology of MS. This impairment causes ability disorder of the parts of the nervous system which are responsible for communication, leading to different symptoms including physical and psychological problems. This study was conducted through a Narrative review using keywords including Multiple Sclerosis, Epidemiology through Search in International Scientific Databases, including: PubMed, Web of Science, Google Scholar and Scopus, and Persian scientific databases including: Barakatkns Knowledge System, Academic Jihad Database, Iranian Medical Library (Medlib), Magiran Database, Knowledge Reference (Civilica), and a search was done on the World Health organization website. In this review study, using keywords such as "pathophysiology" and "multiple sclerosis".

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Introduction

Multiple sclerosis (MS) is one of the most important debilitating diseases in which the myelin sheaths of nerve cells in the brain and spinal cord are damaged. This impairment cause ability disorder of the parts of the nervous system responsible for communication that can cause many symptoms, including physical, psychological and, in some cases, psychiatric problems (1). The cause of MS is unclear, although it is believed to be caused by a combination of environmental factors including microbial and genetic factors. MS is usually diagnosed on the basis of signs, symptoms, and results of medical tests (2). Previously there was no specific treatment for

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MS until Canadian researchers succeeded in treating it. Existing treatments are performed to improve body function after each attack and to prevent new attacks (3). Although the medications prescribed for the treatment of MS are slightly effective, they have side effects and are difficult to tolerate. Although there is no evidence of the efficacy of alternative MS therapies, many people seek these treatments (4). Predicting the long-term outcome of treatment is very difficult, but the most acceptable outcome is seen in women, those who are younger, those who have recurrences, and those who have experienced fewer attacks in the early stages (5). Life expectancy of people with MS is 5 to 10 years lower than others (6). Since 2008, 2 to 2.5 million people around the world have been got MS, while the rates of disease vary widely in different parts of the world and across communities. The disease typically occurs at ages 20 to 50 years and in women it happens twice as much as men (7). The name "multiple sclerosis" is referred to ulcers (staining or in other words plaque or ulcer) that are found in the white matter of the brain or spine. The three main features of MS are lesions in the central nervous system (also called plaques), swelling, and destruction of the myelin sheath of neurons (8). These features interact in a complex and yet not fully understood way to cause nerve tissue degradation and produce signs and symptoms (9). In addition, people believe that MS is a mediated immune disorder that develops as a result of an individual's genetic interaction with environmental factors that are still unknown (2).

Studies show that at least part of the damage is caused by an attack on the nervous system by one's own immune system. MS is more common in women than in men. The disorder is most often diagnosed between the ages of 20 and 40, but can be seen at any age. MS is caused by damage to the protective lining around the nerve cells called the myelin sheath. When this nerve covering is damaged, the speed of the nerve signals decreases or stops (10). The treatment and management of MS is mostly performed using immunosuppressive agents. The aim of this study was to review the pathophysiology of MS by identifying the factors and course of the disease to improve treatment strategies.

Methods

This study was conducted through a Narrative review using keywords including Multiple Sclerosis, Epidemiology through Search in International Scientific Databases, including: PubMed, Web of Science, Google Scholar and Scopus, and Persian scientific databases including: Barakatkns Knowledge System, Academic Jihad Database, Iranian Medical Library (Medlib), Magiran Database, Knowledge Reference (Civilica), and a search was done on the World Health organization website. Unrelated articles and references were excluded and references related to our review were studied.

Results

MS is a common disease of the central nervous system in humans and an autoimmune disease. The disease is chronic. MS often affects young adults and occurs two to three times more in females. In MS myelin of the nervous system is damaged. The disease is characterized by multiple lesions in different regions at different time and recurrent symptoms. That is, one neurological symptom improves after a while and at the other time same symptom or other symptoms occur again. Symptoms of any attack are partially remedied, but recurrent disease may result in a gradual disability (11).

In MS, the clinical symptoms depend on the location and extent of the lesion, and myelin degradation usually results in certain areas such as the optic nerve, brainstem, cerebellum and white matter of the brain hemispheres leading to a series of clinical symptoms in the form of sudden blurred vision, inability to move limbs, lack of balance, duplicity, sensory disturbances are characterized by a feeling of numbness in limbs and other various symptoms (12). The course of the clinical signs of MS differs in

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each patient and can occur as a completely benign disease and the patient is free of neurological symptoms for many years or a rapid progressive state occurs in clinical symptoms associated with disability (13).

Causes

The cause of this fatal disease is not known yet. Researchers believe that hereditary, nutritional and environmental factors may be involved. But some theories have emerged for the emergence of MS. The most accepted theory of the cause of MS is considered an autoimmune mechanism, in that an environmental factor such as viral infections stimulates the immune system and forms antibodies against the myelin of the nervous tissue, thereby destroying the nerve myelin and leading to nervous symptoms (14). MS is a disease with purported environmental causes. Consistent correlations have been found in various settings for latitude, smoking exposure, sunlight, and vitamin D deficiency. Genetic factors can influence a person's susceptibility to the disease. The highest incidence of MS is in the white population, and the disease is less common in the yellow and black. Although genetic susceptibility explains the clustering of MS cases within families and the sharp decline in risk with increasing genetic distance, it cannot fully explain the geographic variations in MS frequency and the changes in risk that occur with migration. Epidemiological data provide some support for the “hygiene hypothesis,” The disease is rarely seen in residents of the equator, but with increasing distance from the equator and in temperate regions of the North and South, such as the US, Canada, Northern Europe and Australia, the disease is more prevalent. Migration to low-prevalence areas before age 15 reduces the risk of developing MS (15).

Outbreak of MS

The occurrence of MS is rare in childhood, but subsequently increases rapidly until it reaches its maximum by the age of 30 years old and remains prevalent until the fourth decade of life and then rapidly declines, so that MS rarely occurs after 60 years. Due to hormonal and immune factors, the incidence of MS in women is 2 to 3 times higher than that of men. MS is commonly seen in the upper socioeconomic classes (16, 17).

Clinical symptoms

Initially, the patient has almost no medical symptoms, but after a few years, the disease develops. Neurologic symptoms in MS are various due to different parts of the central nervous system (CNS) that involved. Due to the nature of the disease and the different parts of the nervous system involved as well as the involvement of geographical factors in how the disease manifests itself, the symptoms and especially the first sign of the onset of the disease and its severity will vary, so in MS disease a classical, fixed form can never be found. Since in MS, the optic nerve, brainstem, cerebellum, and spinal cord are most commonly involved, clinical manifestations of lesions are in these areas (18, 19).

The most common symptoms at the onset of the disease are motor weakness, tingling, vision impairment, sudden blurred vision in one eye (optic neuritis), diplopia, involuntary eye movement, impaired word understanding, tremor, deep sensory impairment and loss of balance, partial paralysis of the lower limbs and changes in emotional responses, feeling cramped or unbalanced, imbalance in the bladder function as a matter of urgency or delayed onset of urination. These symptoms are often transient and resolve within days to weeks, but over time these symptoms may become established and the patient may sometimes have speech, cognitive, mood, and memory problems (20, 21).

The rapid progression of the disease is rarely seen, and in most patients the course of the disease is benign and the symptoms are so mild that they do not even go to the doctor.

Course of the disease

MS is associated with complete or near-complete remission in the early stages of relapse. The time between the first attack and

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subsequent neurological symptoms may be months to years, after this duration new symptoms appearing or recurring. The risk of recurrence after infection and in women about the first three months after delivery increases (22). In some patients, over time and after several relapses and incomplete recovery, the patient may progress to varying degrees of limb weakness, muscle stiffness, sensory impairment, gait imbalance, and urinary problems. Usually the patient survives for up to 30 years after the onset of the disease, and few die at the outset (23).

The course of the disease has many forms, and most patients suffer from exacerbated and relieved symptoms and no symptoms between attacks. Others develop a chronic, progressive form of MS, and their symptoms increase over time. Accordingly, MS has three types of course: 1- recurrent - remedial that disease does not progress between attacks, 2- Secondary progressive: characterized by gradual progression after a period of recurrence and primary recovery, and 3- Primary progressive in which the disability progresses gradually from the beginning (24).

Methods of diagnosis

The diagnosis may be unclear at the onset of MS but gradually, the myelin disappears or the disease recurs, diagnosis will complete. Brain loss and atrophy can be detected by MRI. The main cause of delay in diagnosis is the long hidden period of the disease, which lasts about 1 to 10 years or more (20).

The diagnosis of MS is made on the basis of clinical signs and course of the disease and a history of exacerbation and alleviation of symptoms, neurological examination findings, and laboratory studies such as cerebrospinal fluid (CSF), Visual evoked potentials (VEP) and central nervous system imaging (MRI). In patients with MS, electrophoretic examination of cerebrospinal fluid (CSF) proteins indicates the presence of specific bands in the IgG immunoglobulin region under the name oligoclonal band. Visual evoked potential (VEP) is prolonged and MRIs show lesions of myelin injury in the brain, brainstem, cerebellum or spinal cord that are round lesions with a defined size ranging from a few millimeters to a few centimeters (25).

Discussion and Conclusion

Myelin is made up of fat and protein and is used to cover and aid in nerve fiber conduction. In MS, plaques (sclerosis) form on the nerve fibers of the central nervous system (CNS). When myelin destroys as a result of plaque formation, nerve fiber conductance reduces or absent. This phenomenon, demyelination, causes nerve messages not sent from the brain. Some nerve fibers, or axons, never recover from the effects of demyelination and are damaged resulting in axonal destruction (2). Demyelination and axonal degradation can affect multiple organs and cause symptoms of the disease. B lymphocyte cells synthesize antibodies that are involved in myelin degradation by differentiating into plasma cells. These protein factors can be seen in the cerebrospinal fluid of MS patients. In addition, these cells are involved in the development of inflammation in the central nervous system by secreting proinflammatory agents such as TNFB and lymphotoxin (26). In addition to inflammation in the CNS, the myelin regeneration process is also impaired in patients with MS. By binding the Fas ligand synthesized by the lymphocytes to the Fas receptor on the oligodendrocyte cells, the apoptosis program of these cells is activated and the population of these cells is reduced and thus demyelination will also face problems (27). In many cases, after the destruction of the myelin, re-myelination occurs, which is a spontaneous healing process during which new myelin is made. In most patients, this healing process ultimately fails, and subsequent demyelination and subsequent axonal loss results in progressive and irreversible defects in the molecular mechanisms involved in myelin injury and its repair (28). Environmental factors such as viral infections, active metabolites, and metabolic stresses by damaging the blood-

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brain barrier facilitate the entry of autoreactive lymphocytes and anti-myelin antibodies from the peripheral circulation into the nervous tissue (29). In the central nervous system, local factors such as metabolic stresses cause overexpression of endothelial adhesion molecules. Following the increased expression level of intracellular adhesion molecules type I (ICAM-1) and vascular adhesion molecules type 1 (VCAM-1) and E-selectin, excessive entry of T lymphocytes into the central nervous system occurs. In addition, matrix metalloproteinase activity facilitates the migration of immune cells by destroying extracellular matrix macromolecules (30). Pro-inflammatory cytokines such as TNF and interferon-gamma are synthesized by T lymphocytes, which lead to express specific surface molecules on lymphocytes and antigen-presenting cells including astrocytes, microglia, and adjacent macrophages (31). Binding of antigenic agents such as myelin basic protein, myelin-associated glycoproteins, oligodendrocytic glycoproteins, protein proteolipid, phosphodiesterases, S100 protein, and alpha and beta-crystalline to specific lymphocytic receptors (TCR) and MHC molecules present on antigen presenting cells (APCs) cause the relevant immune responses (32). The type of response created depends on the type of binding between surface molecules with ligands B7-2, B7-1 (33). If anti-inflammatory factors such as IL4 and IL10 are secreted from TCD4 + cells, they can proliferate the Th2 cells. CD4 + T lymphocytes exert their effect on B lymphocyte by interleukin secretion and also stimulate immune responses by stimulating the synthesis of interfering antibodies in myelin repair. Activating of antigen presenting cells, the secretion of interleukins 12 and interferon-gamma activates T helper cells type 1. These cells and interferon-gamma cause damage to myelin, oligodendrocytes and TNF-producing (34). With the destruction of myelin, axons become sensitive to soluble agents such as cytokines and proteases and axonal damage occurs.

Several mechanisms are involved in promoting the repair of damaged myelin. These mechanisms include spontaneous suppression of immune responses and myelin regeneration, increased number of sodium channels in the node of Ranvier and covering myelin-deficient fragments, secretion of antibodies against myelin sheath, and proliferation, migration, and differentiation of oligodendrocyte precursor cells (35, 36). Negative selection in the thymus is an incomplete process and some autoreactive T-cell clones escape central tolerance. To overcome the potential danger of these cells, there are strategies in environmental tolerance that will be a major strategy for maintaining immune tolerance. Reports and research indicate that MS patients have functional deficits. This potential role in the control of autoimmunity in the central nervous system of animal models has been well established (37, 38).

The vast majority of CD4 + CD25 + Treg cells contain FOXP3 transcription factor, which plays a major role in the development and function of these cells. CD4 + CD25 + FOXP3 + Treg cells comprise two major classes known as iTreg and nTreg. nTreg cells in the thymus produce and evolve, which inherently express FOXP3. iTreg cells arise from naive T cells due to antigen stimulation and the presence of TGF-β. Induction of FOXP3 expression by TGF-β depends on activation of SMAD3 transcription factor, which in conjunction with TCR-induced NFAT binds to the FOXP3 Enhancer region and induces the chromatin remodeling required for POXP3 transcription. Signaling through Akt-mTOR can inhibit SMAD3 activity (39, 40).

Recent studies have shown that in MS patients CD4 + CD25 + FOXP3 + Treg cells are normal in number but impaired in function. The discovery of a new protein called GARP or LRRC32 revealed that FoxP3 is not a fully specific marker for CD + CD25 + FOXP3 + Treg cells, and that CD4 + CD25-Treg cells express FOXP3 by TCR-mediated antigen stimulation. Thus, a more specific marker needs for CD4 + CD25 +

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Treg cells or an adaptive system to investigate the quantitative and qualitative differences in FOXP3 expression in CD4 + CD25 + Treg cells compared to normal T cells (41). GARP protein mediates the expression of FOXP3 and is highly expressed in activated Treg cells, and enables Treg cells to inhibit the activity of activated T cells. GARP + Treg cells have greater inhibitory potency than GARP-Treg cells and inhibition of GARP expression by SiRNA decreases the inhibitory potency of Treg. Therefore, this molecule can be used to specifically identify CD4 + CD25 + Treg cells, especially activated CD4 + CD25 + Treg cells, and to investigate the inhibitory potency of these cells. Since Akt-mTor pathway by inhibiting of SMAD3, can decrease FOXP3 expression and subsequently GARP expression, and according to studies on the effect of mTOR on Treg cells, by mTOR inhibition, the number of Treg cell as well as inhibitory potency of these cells Increased (42). Despite modern studies, the true cause of the disease has not yet been determined and therefore there is no definitive cure for the disease (27, 43). But developing and following a specific treatment plan and using new therapies and rehabilitation techniques can alleviate the symptoms, slow down the progress, preserve and enhance one's ability with support the current situation.

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Conflicts of interest

The authors declare that there is no conflict of interest regarding the publication of this article.

Authors' contributions

Study design: A.K.A., S.M.M.H., A.A.A.
Writing: H.N., P.S.
Final revision: All authors

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