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Multiple Sclerosis: A Comprehensive Review of Etiology, Immunology, Pathogenesis and Treatment: (Article Review)

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ABSTRACT

Background: *Multiple Sclerosis (MS) is a chronic, immune-mediated inflammatory disease of the Central Nervous System (CNS), characterized by the destruction of the myelin sheath that insulates nerve fibers. This demyelination impairs the transmission of electrical signals, leading to a broad spectrum of neurological deficits. MS primarily affects young adults, with a higher prevalence in women this review focus on etiology ,immunology ,pathogenicity and treatments of MS. The exact cause of MS remains unknown, but it is widely accepted as a multifactorial disease resulting from a complex interplay between genetic Predisposition associations with specific human leukocyte antigen (HLA) alleles, particularly HLA-DRB1*15:01, increase susceptibility, Environmental Triggers: Factors such as low Vitamin D levels, cigarette smoking, and obesity during adolescence are linked to higher risk and Infectious Agents. MS is primarily driven by a breakdown in immune tolerance. Peripheral Activation including autoreactive T-cells (specifically Th1 and Th17) and B-cells are activated in the periphery and migrate across the Blood-Brain Barrier (BBB). Inflammatory cascade inside the CNS, these cells secrete proinflammatory cytokines and recruit macrophages. B-cells contribute via antigen presentation, cytokine production, and the formation of oligoclonal bands (antibodies found in the cerebrospinal fluid). Pathogenesis of MS is the formation of demyelinating plaques within the white and gray matter of the brain and spinal cord. The immune system attacks oligodendrocytes (myelin-producing cells), leading to focal areas of myelin loss while initially considered a disease of myelin, permanent neurological disability is caused by axonal transection and neurodegeneration, which can occur even in early stages. there is currently no cure, management focuses on two pillars including acute relapse management which high-dose corticosteroids (e.g., methylprednisolone) are used to reduce inflammation and accelerate recovery from flare-ups and Disease-Modifying Therapies (DMTs) ,these target the underlying immune response to reduce relapse frequency and slow disability progression.*

Keywords: Multiple Sclerosis, *Disease-Modifying Therapies (DMTs)*, *Proinflammatory cytokines*.

Article Information

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1.INTRODUCTION

Multiple sclerosis (MS) is an inflammation neurological condition of the central nervous system (CNS) characterized by gradual degradation of the sheath of myelin, which often causes sensory, motor, and cognition impairment [1]. Based to the

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Atlas of MS, this unexpected syndrome affects roughly 2.2 million individuals worldwide in various clinical forms and presentations [2]. The idea that adults between the ages of 20 and 40 are more prone to the illness, with a greater prevalence in females than males, is supported by several statistics. MS is believed to be the result of genetic and interactions with the environment, despite its poorly understood causation [3].

Environmental variables include cigarette smoking, illnesses, and, specifically, dietary vitamin D or ultraviolet B radiation (UVB) exposure [4-6]. There are multiple genetic variables associated with MS that are thought to contribute to the start of the disease via immunologic significant genetic risks [7]. On the opposite, HLA genes are thought to have the greatest genetic risk variation for M.S [8]. Extended haplotypes spanning HLA classes I and II have consistently been shown to be of significant interest due to their association with the risk of a number of autoimmune disorders [9]. However, a significant portion of multiple sclerosis is caused by non-HLA genes, such as those that may affect different immunological organs and cell types [10]. HLA-DRB115:01 has become the main genetic risk factor for multiple sclerosis among the HLA class II alleles [11]

The main purpose of the HLA complexes is to help the immune system differentiate between self and non-self. Differences in HLA genes may cause self-antigens to appear, which would then cause the autoimmune reaction that characterizes multiple sclerosis [12]. IL7R (interleukin-7 receptor α gene), one of the specific non-HLA-associated genes linked to multiple sclerosis, is involved in immune cell proliferation and survival; a specific variant in this gene results in the creation of a soluble receptor. SNPs in the gene (IL2RA), which is important in immunological control, have been linked to an increased risk of multiple sclerosis [13].Variations in the gene known as TNFRSF1A (Tumor necrosis factor receptor superfamily member 1A), which controls inflammatory processes, have been connected to an increased risk of multiple sclerosis [14]. T helper (Th)1 rather than Th2 CD4+ T cells can effectively infiltrate MS lesions when IL-16 is secreted within the central nervous system (CNS). Its association with inflammation, the degree of axonal damage, and the severity of the disease was demonstrated in earlier research, indicating that IL-16 plays a role in the pathophysiology of MS [15].

2.Etiology and epidemiology

The etiology of multiple sclerosis is often described as unclear or unknown, a description that is not entirely accurate given its significant impact on the elderly. Epstein-Barr virus, sunlight (UV-B radiation), smoking (including hookah smoking), vitamin D levels and other related vitamins, as well as the patient's family history and inherited genetic traits, all play key roles in the pathogenesis leading to the development and progression of multiple sclerosis [16]. Migration studies clearly indicate that multiple sclerosis is secondary to many factors, including an external triggering factor [17].Older migrants from lower-risk nations, for example the West Indies, are less likely get MS than kids borne to migrants in Europeans.

Migratory studies reveal that the environment takes precedence over heredity, emphasizing the importance of preventative research focusing on recognized environmental risks. Being really EBV negative protected against MS [18, 19], whereas symptom infection with EBV (infectious mononucleosis) also doubles the risk of MS [20]. There is conflicting evidence about how EBV raises the risk of MS; the

molecules has long been a widely accepted theory [21]. recently, shows, think that B-cell immortalized as well as transformation brought on by EBV is a major factor in the appearance of illness [22].

M S is becoming a worldwide illness [23]. Which a prevalence rises the longitude, this variation has been decreasing in Norway and the United States, the two nations where it has been examined [23]. The longitudinal gradient in the prevalence of MS is significantly linked to UVB radiation, the production. which promotes cutaneous vitamin D (vD), Low vitamin D levels, lower vitamin D consumption, decreased outdoor activity, and increased MS susceptibility have all been linked to genetic variants that cause low vitamin D levels [24].

Multiple sclerosis affects more women than men, although this was occasionally the case. In series of cases from the early 1900s, the gender ratio was nearly equal. Since that time, the gender ratio has progressively increased, reaching around 3:1 (F:M) in most affluent countries [25]. Tobacco use, which raises MS risk by about 50%, can account for as much as 40 percent of the higher rates of MS in women [26]. Few women smoked before World War II, but as the prevalence of MS in women raised, so did the number of women who smoked after the conflict ended [26].

The idea that chemical solvents [27] and smoking cigarettes [28], Unlike oral smoking or sniffing [29], are connected to multiple sclerosis (MS) originates from the fact that these chemicals cause subsequent translational changes via the presentation of antigens that takes up residence in the lung tissueThe likelihood of having MS modulation most likely begins from pregnancy and persists throughout life. The month-of-birth impact and higher consistency in twins with dizygotic syndrome compared to sibling indicate that the intrauterine environment has a significant role in predicting MS risk, albeit it is unclear if this is due to related circumstances, epigenetic mechanisms, or both [16]. MS susceptibility is influenced by genetics; approximately one in eight individuals have an extended family history of the disease [30].

In the United Kingdom and Canada, female monozygotic twin concordance is close to 30%, whereas in southern Europe, it can be as low as ~8.5% [31]. HLA-DRB1*15 and other sites in significant relationship disequilibrium with this allele are the principal hereditary factors responsible for multiple sclerosis. [32]. Although the mechanism is still unknown, heterozygotes for HLA-DRB1*15:01 have an odds ratio of MS >3 and homozygotes >6 32. The protective benefits of class 1 alleles, such as HLA-A*02:01, are not explained by the hypothesis that HLA-DRB1*15:01 functions through antigen presentation [33].

Over 150 polymorphisms of one nucleotide linked to MS susceptibility have been found through association research conducted across the genome [34]. For most of these, the odds ratio is low, between 1.1 and 1.2. Numerous single nucleotide polymorphisms are found near immune function-related genes, usually in regulatory rather than coding areas. Among the functional variations found are those in T N F R1 [37], B A F F [38], CYP2 R1 [39], IL7 R [35], IL 2RA [36], and TNFR1 [37]. Obesity [42] and vitamin D [39–41] have been shown to be independent risk factors for disease by Mendelian randomization experiments.

3.Immunology of multiple sclerosis

MS is characterized by inflammatory lesions and demyelinating plaques in the central nervous system, a system that consists of immune cells... These lymphocytes aggregate around veins to form perivascular cuffs after passing through post-capillary

venules and venules into the perivascular area [43]. You know what? Persistent lesions, which are defined by collections of B cells called follicles and are not like the perivascular cuff seen during the early stages of inflammation [44].The adaptive immune, immune cells T.lymphocyte and B. lymphocyte .are known to be major factors in the pathogenesis of MS but further studies have emphasized the key role of innate lymphoid cells and myeloid cells. You know what? Immune cells that promote neuroinflammation in MS are discussed below.

3.1.Adaptive immune cells: T and B cells

Initiating and sustaining an autoimmune reaction against the nervous system's nerves is largely dependent on auto-reactive T cells, particularly (CD4+) T cells. Oh, and they see myelin and myelin antigens which are vital parts of the myelin coating and include myelin basic protein, myelin protein (MBP), myelin lipoprotein (PLP), and myelin oligodendrocytes glycoprotein (MOG) [45]. When these self-antigens are recognized, autoreactive T cells are activated, which causes them to proliferate and differentiate into effector T cells [46]. The nervous system's center is probably not the site of seriously primary reactions to these autoantigens [47].

In addition to being impacted by chemokines that activated T cells migrate across the blood-brain barrier by upregulating endothelial cell adhesion molecules such vascular cell adhesion molecule-1 (VCAM-1) and intercellular adhesion molecule-1 (ICAM-1) [48–49]. After entering the central nervous system, self-reactive T lymphocytes release cytokines that promote inflammation such as tumor necrosis factor (TNF) and interferon-γ (IFN-γ), which start a chain reaction of inflammation [50].. This inflammatory environment also aids in the disintegration of the brain- blood separation, which permits extra immune cells to enter the CNS [51]. Additionally, CD8+ T lymphocytes have the ability to identify CNS leading antigens, This may cause cytokines associated with inflammation to be released, enhancing the immunological response [52] and kill oligodendrocytes and axons by releasing granzyme and perforin [53]. The chronic character of multiple sclerosis is sustained by a self-reinforcing cycle of severely ongoing inflammation and neural degeneration. Like Plus Tregs are essential for immune response modulation and a peripheral tolerance maintenance [46] whereas in MS, Tregs malfunction and help break down immunological tolerance by generating more IFN-γ and decreasing suppressive activity [54], which permits a persistent attack on myelin [55].

B cells have a variety of functions, including generating antibodies against myelin components including MBP and MOG [56] and serving as cells that present antigen (APCs). The immune system complexes that are formed by these autoantibodies trigger complement cascades, induce inflammation, and ultimately result in demyelination [57]. B cell dysregulation is indicated by the presence of these autoantibodies in the central nervous system.

Furthermore, B cells engage in interactions with T cells and encourage the provocation of myelin antigen-specific auto -reactive lymphocytes [58]. Indeed, this process leads to the development of MS through sustaining the immunological response and the central nervous system's ongoing inflammation. Furthermore, regulatory B cells, also known as Breg cells, have the capacity to govern the immune response. However, in multiple sclerosis, these cells are dysregulated, which impairs their capacity to inhibit proinflammatory reactions, hence intensifying the autoimmune assault on myelin [59]. And

yes, immunological homeostasis depends on the balance between pro-inflammatory and regulatory B-cell functions, and disruption adds to the chronic inflammation seen in multiple sclerosis. [60,61].

3.2.Innate immune cells have contributed to the development of MS

Monocytes aid in the phagocytoses of myelin and myelin detritus in multiple sclerosis, which presents myelin antigens to T cells and boosts the adaptive immune response. There are three primary subgroups of monocytes that have distinct functions: mesenchymal (CD14++CD16+), traditional (CD14++CD16), and non-classical (CD14+CD16++) [62]. Classical monocytes have the ability to enter the central nervous system and aid in the removal of myelin waste. However, by producing cytokines that are pro-inflammatory and encouraging the activation of additional immune cells, they can potentially make inflammation worse [63]. The production of inflammation-related cytokines and by mesenchymal monocytes contributes to the pathophysiology of multiple sclerosis. Because of their increased potential to present antigens, these cells help to activate autoreactive T cells and maintain the integrity of intermediate monocytes, which have been linked to the pathophysiology of multiple sclerosis by producing inflammatory cytokines and chemokines. These cells have a greater ability to deliver antigens, which helps activate autoreactive T cells and sustain the process of inflammatory responses in lesions associated with MS [64].

MS lesions' inflammation cascade [64]. Non-classical monocytes participate in vasculature patrols and immunological surveillance [65]. Through the destruction of cells that have died and the generation of pro-inflammatory cytokines, it may be linked to the resolution of inflammation in MS [66]. However, non-classical monocyte deregulation leads to a weak resolution of inflammatory conditions. Classic monocytes mature into macrophage and take on a pro-inflammatory character once they penetrate the central nervous system [67]. TNF and IL-1, two cytokines released by activated macrophages, worsen the inflammatory environment and add to the demyelination seen in MS lesions [68]. One important element in the pathophysiology of multiple sclerosis is the disruption of the balance between M1 and M2 macrophages. The development of inflammation and demyelination is facilitated by an overabundance of M1 polarization. M1 to M2 polarization changes as the illness worsens in order to reduce inflammation and encourage tissue healing [69].

The immunological response to CNS antigens is initiated and modulated by dendritic cells (DCs). As APCs, DCs and follicular DCs (FDCs) in the perivascular space of the central nervous system (CNS) and peripheral lymphoid organs deliver myelin-derived antigens to activate autoreactive T lymphocytes [70]. The demyelination seen in MS lesions is a result of activated T lymphocytes migrating into the central nervous system and sustaining inflammation [71] Additionally, DCs are involved in immunological tolerance maintenance, and changes in DC activity might cause self-antigens to present immunogenically [72], aggravating immune-mediated responses [73].

Dendritic cells, also known as DCs, serve a critical function in immune monitoring by identifying and removing infected or altered cells without prior sensitization. DCs are involved in the activation and control of autoimmune NK cells, which are cytotoxic cells [74,75]. Studies on multiple sclerosis have revealed variations in the quantity and activity of natural killer (NK) cells in the peripheral blood and central nervous system,

which may indicate dysregulation of NK cell activity [76].By affecting the stimulation and differentiation of T cells implicated in the formation of MS lesions, NK cells can modify the immune system's adaptive response [77]. A heightened autoimmune reaction against myelin constituents results from the disparity between the number of effector T cell and regulating T cells caused by malfunctioning NK cells [78].

4.Pathophysiology of multiple sclerosis

MHC complex identified unidentified antigens (AG) can cause T lymphocytes to evolve into autoreactive to antigens. II. There are serious class compounds that have the potential to cause inflammation. This has been demonstrated to be important in how AGs are presented to T cells [79,80]. The primary cells that present antigen (APCs) are dendritic cells and macrophages (Mφ), but other cells, like the oligodendrocyte progenitors, also have a particular purpose. T cells are activated when AGs are presented by APCs in conjunction with MHC molecules. Both matrix metalloproteinase (MMP) activity and APC functionality can be impacted by Na+ concentrations. When T cells' α4β1 integrin (very late antigen 4) attaches itself to APCs' vasculature adhesion molecule-1, both T cells and APCs migrate to AG locations. Additionally, α4β1 integrin (very late antigen 4) can be bound by immunoglobulin antibodies and its movement inhibited [81].

T lymphocyte cells that are autoreactive multiply and expand within lymphoid organs. They finally reach the bloodstream after being stimulated by sphingosine-1-phosphate. T cells start generating MMPs when they attach to increased adhesion molecules. The blood-brain barrier then breaks down as a result of the MMP. When they encounter APCs in the central nervous system, they start to split apart. Helper T cells undergo myelin damage and differentiate into two subtypes: antiinflammatory traits Th2 cells and inflammatory (Th1) cells. Mφ cells and microglia are attacked by cytokines released by Th2 cells.. Autoreactive T cells begin to produce antibodies against B cells that cross the damaged, damaged part of the blood-brain barrier essentially resulting in the formation of auto _antimyelin antibodies. Furthermore, studies have shown that anti-B cell antibodies trigger a cascade of complement and complement reactions that repeatedly enter and attack myelin. It is highly probable that these relapses are caused by immune-mediated inflammatory processes. Targeting these immune-induced inflammatory processes is central to all current treatments and cures for multiple sclerosis[82]

5. Multiple Sclerosis Treatment

Potential induction treatments have been the subject of numerous clinical trials. immune-suppress like methotrexate and cysteine were frequently utilized in the initial stages of MS therapy. Due to insufficient phase III research, Cysteine has not been officially approved for use in treating multiple sclerosis, as studies have shown that it has only been used outside of approved uses or in recognized clinical trials. A member of the anthracycline class, methotrexate is an antineoplastic compound and derivative of an anthracycline. Although this regimen may vary, The standard dose is given IV at a dosage of twelve mg/m² each 3 months, with a extreme dose of 140 mg/m². Due to the possibility of severe adverse effects, methotrexate use has decreased in the last few years [83].

In patients with relapsing-remitting multiple sclerosis (RRMS) and secondary progressive multiple sclerosis (SPMS) with high activity.Many tests were conducted on methotrexate, including a three years. MRI and clinical study and on several patients with

aggressive multiple sclerosis, which has been clearly established as people who exhibit multiple lesions on gadolinium-enhanced MRI and have had more than two relapses in the preceding year [84]. One hundred and nine patients were randomly assigned to two groups.

The first group, consisting of 54 patients received (12 mg/m²) and (20 mg/ m²)) from MTX each month doses with 1 gram of methylprednisolone for 6 months repeatedly, f followed within the previous twenty-seven months by (IFN). In addition to receiving 1 gram of methylprednisolone per month for the first six-month duration of treatment, the second group of 55 patients also received interferon beta-1b (a dosage of 250 mg subcutaneously every day for three years The time it took for the EDSS scale to degrade by a least one percentage point was the main endpoint confirmed after three months.Clinical and demographic characteristics were similar between the two patient groups at enrollment. At enrollment and at months 9, 24, and 36, patients had a rotational echocardiography in addition to a thorough neurological assessment each thirty days. The time to at least one point worsening on the EDSS scale, The diagnosis was confirmed after three months, with an 18-month delay in onset observed in the methotrexate group compared to the interferon group ($p < 0.012$).

The risk of disability progression after three years was also decreased in 65 percentage with the methotrexate group compared to the interferon group (11.8% vs. 33.6%). Research showed that the percentage of patients who did not relapse increased ($p < 0.008$). in the methotrexate group. Patients treated with methotrexate also showed a 61.7% declining in the relapse rate, a decrease in the number of gadolinium-enhanced lesions at month nine, and a slower rate of new T2 lesion accumulation at each time point [85]. In another measured study [82], 40 patients with relapsing- who had 1–15 gadolinium-enhanced lesions found on MRI and Expanded Disability Status Scale (EDSS) scores of 0–6.5 were randomly assigned to receive either shorter-term initiation methotrexate therapy at 12 and 15 months, according to a different study group. The relapse rates were 0.16 and 0.32 in the methotrexate-GA and GA group respectively. During the fifteen month study, eighty one percentage of MTX-GA patients group and 79% of GA patients remained free relapse free [83].

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