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Multiple Sclerosis (MS): Overview, Pathophysiology, Diagnosis, and Pharmacological Management-An Updated Review

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Abstract:

Background: Multiple sclerosis (MS) is a chronic, immune-mediated inflammatory disorder that affects the central nervous system (CNS), causing demyelination and neurodegeneration. Its pathophysiology involves the immune system targeting the myelin sheath, leading to a range of neurological impairments. MS is marked by relapsing-remitting episodes, with a significant burden on individuals and society. Although the understanding of MS has advanced, it remains a challenging condition to treat.

Aim: This review aims to provide an updated understanding of MS, including its etiology, pathophysiology, diagnosis, and pharmacological management.

Methods: A comprehensive review of current literature on MS was conducted, focusing on recent developments in pathophysiology, risk factors, and emerging treatments. Key areas of research include the genetic and environmental factors influencing disease onset, advances in diagnostic techniques, and the effectiveness of current pharmacological therapies.

Results: MS is influenced by a combination of genetic susceptibility and environmental triggers, with notable geographic and demographic variations. Recent advancements in diagnostic criteria, including the use of biomarkers like oligoclonal bands, have improved early diagnosis. Pharmacological treatments have evolved, with new immunomodulatory therapies showing promise in clinical trials. However, MS remains difficult to treat, with no definitive cure.

Conclusion: MS is a complex autoimmune disease with significant variability in its presentation and progression. Continued research is needed to better understand its pathophysiology and to develop more

effective, personalized treatments. Improved diagnostic methods and new drug therapies hold promise for better management, though challenges remain in providing optimal care.

Keywords: Multiple Sclerosis, Pathophysiology, Diagnosis, Pharmacological Management, Autoimmune Disease, Demyelination, Immune System.

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Introduction:

Multiple Sclerosis: A Comprehensive Review

Multiple sclerosis (MS) is an immune-mediated inflammatory disorder that impacts the myelinated axons of the central nervous system (CNS), leading to varying degrees of damage to both the myelin and the axon. The condition is characterized by inflammation, neurodegeneration, and gliosis, which are the definitive pathological hallmarks of MS. Perivascular lymphocytic infiltration, alongside macrophage activity, leading to the deterioration of the myelin sheaths encasing the neurons [2,3]. Multiple sclerosis typically has a relapsing-remitting pattern, marked by episodes of neurological deterioration that may completely or nearly completely resolve. The pathophysiology of multiple sclerosis remains incompletely understood, though it is thought to involve a combination of genetic predisposition and a potential non-genetic trigger, resulting in chronic autoimmune attacks on the central nervous system. The recorded geographical variations in MS incidence suggest that environmental factors may substantially affect the manifestation of the disease [3,5]. Recent advancements in diagnostic criteria facilitate faster and more precise diagnosis for individuals [4]. Recent improvements in understanding the core mechanics of MS have enabled the development of novel therapeutic options [5,6]. Numerous pharmaceuticals have shown promise in Phase III clinical trials, indicating that approval is forthcoming [7]. The proliferation of therapy options for MS complicates the process of identifying the appropriate treatment for each patient. Contemporary therapy methods include the use of hormones, immunosuppressants, plasma exchange, and several other pharmaceutical treatments [8]. Despite these advancements, multiple sclerosis remains clinically untreatable, putting significant physical, mental, and societal burdens on affected individuals and their communities [9]. Consequently, the secure and efficient management of multiple sclerosis has emerged as a substantial medical challenge necessitating increased attention [3,10]. This study seeks to examine the history, etiology, and pharmacological interventions associated with multiple sclerosis (MS).

History

The term "paraplegia" typically refers to any significant neurological disorder that hinders motor function. The initial documented reference to what is currently identified as multiple sclerosis (MS) dates to Saint Lidwina of Schiedam, a historical figure from the Netherlands in the late 14th century [11,12]. Augustus d'Este, who diligently chronicled his disease for 26 years, detailed the gradual exacerbation of symptoms today recognized as multiple sclerosis. At the age of 28, his primary symptom was optic neuritis, leading to transient vision impairment. At the age of 54, he had acquired considerable motor deficits that profoundly affected his capacity to walk [11-14]. Jean-Martin Charcot's contributions to the definition and classification of multiple sclerosis established a vital framework for comprehending the condition and set the groundwork for subsequent progress in the discipline. His students then correlated the clinical signs of the disease with post-mortem lesions, providing additional understanding of the pathophysiology of MS. Joseph Babinski's 1885 thesis on multiple sclerosis presented comprehensive descriptions of plaques located in the brain and spinal cord, whereas Pierre Marie's research highlighted autonomic dysfunction and gait problems in patients with multiple sclerosis [11,15]. In the mid-19th century, Ernst Leyden was one of the initial proponents of a possible hereditary aspect of multiple sclerosis, a notion further developed in the 1930s by Curtius and associates in Germany, who commenced the examination of genetic patterns and familial clustering of the disease [11,13,14]. During the late 19th and early 20th centuries, prominent individuals like Charcot, Von Frerichs, and Vulpian identified multiple sclerosis as a distinct and identifiable clinical condition [12,15]. During that period, multiple sclerosis cases were classified according to histological findings, clinical manifestations, and prognosis, leading physicians worldwide to diagnose and

categorize the disorder more systematically [13,14]. As awareness of multiple sclerosis increased, so did the formulation of diverse hypotheses concern its genesis and management. A seminal 1935 study investigated 158 distinct treatments for multiple sclerosis, encompassing anticoagulants, histamine desensitization, specific diets, vaccinations, and anticancer medications [13,16]. In subsequent decades, the stringency of randomized clinical studies intensified, supported by improvements in disease classification and impairment metrics. This time witnessed the development of ideas elucidating the immunological, genetic, and environmental components associated with MS, along with the geographical variations in its occurrence [6]. Multiple sclerosis advocacy organizations significantly contributed to the advancement of research and public education, while also transforming societal perceptions of the condition [16,17]. Recent years have witnessed substantial advancements in fundamental research, elucidating the etiology and processes of MS, alongside the introduction of immunomodulatory therapies [11,16,17].

Etiology

The onset of multiple sclerosis (MS) is affected by numerous risk variables, including age, sex, race, genetics, geography, and infections such as herpes simplex, chlamydia, and rabies [18,19]. Multiple sclerosis is thought to arise from a complex interplay of genetic predispositions, environmental variables, and nutritional impacts [6,20]. Multiple sclerosis (MS) fundamentally arises from an autoimmune assault on the central nervous system (CNS), triggered by immune system activation. A variety of mechanistic paths have been suggested, with the "outside-in" approach becoming increasingly prominent. This concept posits that an unidentified antigen activates proinflammatory CD4+ T-helper cells (Th1 and Th17), resulting in endothelial adhesion within the CNS, disruption of the blood-brain barrier (BBB), and ensuing immune-mediated injury via cross-reactivity. Conversely, the "inside-out" paradigm asserts that inherent dysfunction within the central nervous system results in inflammation-induced tissue damage [21]. The impact of environmental factors, especially the latitudinal gradient of multiple sclerosis prevalence, has been extensively investigated [22]. Vitamin D deficiency has been suggested as a contributing factor to the increased frequency found in persons living at higher latitudes [23,24]. Moreover, genetic factors are pivotal, as a family history markedly elevates the chance of having MS, with heritability estimates between 35% and 75% [25,26]. The human leukocyte antigen DRB1*1501 is significantly correlated with multiple sclerosis (MS) [27].

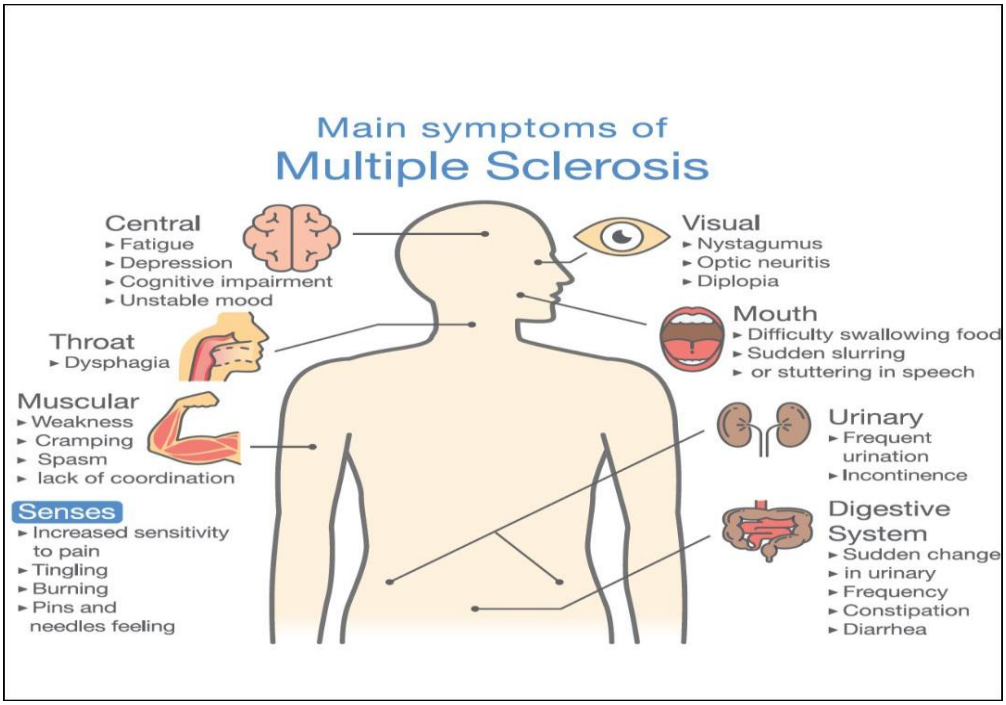

Figure 1: Multiple Sclerosis Clinical Presentation.

Risk Factors

- **Vitamin D Deficiency**: Vitamin D is recognized for its critical role in modulating lymphocyte activity, growth, and immune responses, suggesting that it plays a significant role in the pathogenesis of MS [19]. Its effects on both the innate and adaptive immune systems have been well documented, with vitamin D shown to reduce the production of Th1-mediated proinflammatory cytokines [28]. Numerous studies have demonstrated that vitamin D supplementation significantly alters the levels of interleukin-10 (IL-10) and interleukin-17 (IL-17) [29,30]. The prevalence of MS is notably higher in regions located farther from the equator, with minimal incidence near the equator and increasing to 50 cases per 1,000,000 individuals in areas 45 degrees north or south of the equator. Vitamin D deficiency among MS patients likely contributes to this geographical distribution pattern [1,20,31,32].
- **Genetics and Family History**: There is compelling evidence suggesting that genetic factors play a role in the predisposition to MS. However, this genetic susceptibility is not straightforward, as no single MS-specific gene has been identified [33,34]. Genetic studies have shown that the risk of developing MS is higher among first, second, and third-degree relatives of affected individuals [35,36].
- **Diseases**: Bacterial or viral infections are thought to trigger the onset of MS in genetically predisposed individuals. Infections during late childhood, in particular, may introduce foreign antigens that activate Th1 cells, thereby initiating the autoimmune processes characteristic of MS [20,31].
- **Injury**: Traumatic injuries to the brain or spinal cord have been considered potential triggers for MS. Such injuries are known to increase the permeability of the BBB, facilitating the entry of Th1 cells into the CNS. This breach of the BBB is thought to initiate the inflammatory response that leads to myelin damage and the formation of MS lesions [37,38].
- **Cigarette Smoking**: Cigarette smoking has been associated with an elevated risk of developing MS. Smokers with MS tend to experience a worse long-term prognosis and have a higher incidence of brain atrophy compared to non-smokers [39]. Furthermore, individuals with MS are more likely to smoke than the general population [40]. MS patients also face a higher burden of comorbid conditions, resulting in a diminished quality of life, increased disability, and higher mortality rates compared to the general population [41,42].

Epidemiology

Multiple sclerosis (MS) is one of the most common neurological disorders worldwide and is the primary cause of non-traumatic neurological disability among younger individuals in many countries [43]. In the United States, over 400,000 persons are impacted, whereas the global prevalence is approximately 2.5 million people. The disease has exhibited a rising prevalence in females, a pattern that has emerged since the early 20th century when the male-to-female ratio was roughly equivalent. In recent years, this ratio has increased, especially in developed nations, and today approximates 3:1 (female to male) [44,45]. Smoking is associated with a 50% heightened risk of getting multiple sclerosis [46]. The usual age of onset varies from 20 to 40 years; however, multiple sclerosis can occur at any age. Approximately 10% of cases are identified before to the age of 18. Multiple sclerosis diagnosed post-50 years of age is categorized as "late-onset multiple sclerosis" (LOMS), but such instances are uncommon [47]. The prevalence of multiple sclerosis is estimated at one in 1,000 among individuals of European descent, with limited evidence for non-European communities, although the frequency seems lower among East Asian and African groups. Recent research indicate that African-American groups exhibit prevalence rates similar to those of European communities [48,49]. The prevalence of MS demonstrates a latitudinal gradient, with elevated rates noted in the northern latitudes of Europe and North America. Moreover, distinct genetic susceptibility variables have been recognized among various human subpopulations, irrespective of geographic location, underscoring the intricate interplay of genetic and environmental influences. Research has shown that individuals who move to areas with elevated MS incidence during infancy are at a greater risk of developing the disease in later life [50,51].

Pathophysiology

Multiple sclerosis is defined by the development of plaques in the central nervous system (CNS), along with inflammation, demyelination, axonal injury, and axonal degeneration. These plaques mostly manifest in the brain and spinal cord, impacting the white matter adjacent to the ventricles, optic nerves and tracts, corpus callosum, cerebellar peduncles, long tracts, and the subpial regions of the spinal cord and brainstem, as well as the gray matter. These plaques are observable in all multiple sclerosis subtypes (primary, secondary, and relapsing-remitting MS), although their presentation fluctuates over time, reflecting significant heterogeneity in the immunopathological patterns of demyelination and oligodendrocyte degeneration between relapsing-remitting and progressive forms of the disease [52,53]. Multiple sclerosis is recognized as an autoimmune condition wherein autoreactive immune cells penetrate the blood-brain barrier and assault the central nervous system. The standard procedure for the removal of autoreactive immune cells transpires during development in the thymus or bone marrow through central tolerance mechanisms that include B cells. Although certain autoreactive cells may bypass this process and reach circulation, peripheral tolerance mechanisms generally inhibit them from inducing disease in the majority of patients. The malfunction of regulatory T cells and the resistance of autoreactive T cells to suppression exemplify processes by which peripheral tolerance may fail. The activity and activation of these autoreactive cells are affected by a complex interplay of genetic and environmental risk factors, which are likely to contribute to illness progression [52,54,55]. The principal T cell subsets implicated in multiple sclerosis include CD8+ T cells, CD4+ Th1 cells, and Th17 cells. These cells generate cytokines including interferon-gamma, IL-17, and granulocyte-macrophage colony-stimulating factors, which may contribute to the etiology of multiple sclerosis [54]. The elevation of immunoglobulin levels in cerebrospinal fluid (CSF) indicates a substantial involvement of B cells in multiple sclerosis (MS). The intrathecal synthesis of oligoclonal immunoglobulins, known as oligoclonal bands (OCBs), serves as a diagnostic feature of multiple sclerosis (MS). In multiple sclerosis, the predominant B cells in cerebrospinal fluid and brain parenchyma are CD27+ memory B cells, which undergo clonal expansion and display somatic hypermutation and class-switched immunoglobulin transcripts. The correlation between the CSF immunoglobulin proteomes and the B cell immunoglobulin transcriptomes indicates that antibody-secreting cells, originating from clonally expanded B cells in the CNS, significantly contribute to the elevated intrathecal clonal immunoglobulin production observed in MS, as demonstrated by OCBs in CSF [54,56].

In multiple sclerosis patients, the meninges are infiltrated by inflammatory B lymphocytes, and a greater burden of these infiltrates is associated with heightened severity of cortical lesions, neurodegeneration, and clinical dysfunction. B cells may serve as reservoirs for Epstein-Barr Virus (EBV) [53,54]. Subsequent to EBV infection, B cells undergo transformation into antigen-presenting cells, hence augmenting their capacity to present antigens. Recombinant human myelin oligodendrocyte glycoprotein was demonstrated to be internalized and cross-presented by Epstein-Barr virus-infected B cells, which were effectively identified by cytotoxic CD8+ T cells. Moreover, B cells from multiple sclerosis patients exhibited elevated CD40 expression, signifying augmented antigen presentation capability. In people with relapsing-remitting multiple sclerosis (RRMS), heightened expression of B cell activation markers is associated with considerable neurodegeneration, as indicated by a rise in T1 hyperintense lesions and a decrease in brain volume. In addition to B-cell-related processes, the impairment of effector T cells also plays a role in the advancement of MS [24]. In healthy individuals, CD8+ cytotoxic T lymphocytes regulate EBV infections by eradicating infected cells. The cytotoxic CD8+ T cells, known as "latency-specific T cells," are specifically primed to recognize and eliminate cells that express EBV latent proteins. During multiple sclerosis exacerbations, the population of Epstein-Barr virus-specific T cells proliferates, and the activity of latency-specific CD8+ T cells escalates. As the disease advances, these latency-specific T cells display a tired phenotype and are unable to suppress the proliferation of latently infected cells, resulting in a feedback loop that exacerbates the accumulation of infected cells, further undermining the autoregulatory system and depleting T cells. This instability may result in repeated relapses, linked to inadequate management of EBV reactivation and heightened infection of naive B cells, hence promoting viral dissemination [24]. Another pathogenic mechanism in multiple sclerosis is B cells presenting antigens to T cells and secreting

deleterious chemicals that destroy oligodendrocytes [54]. Furthermore, microglia and macrophages release various cytokines, including tumor necrosis factor (TNF)-α and interleukin (IL)-1β, which may facilitate neurodegeneration via mechanisms such as cytokine-mediated cell death, suppression of astrocytic glutamate reuptake, and the activation of aberrant ribonucleic acid-binding proteins. These cells can also secrete glutamate, perhaps exacerbating excitotoxicity and promoting more neurodegeneration. Additionally, microglia and macrophages produce reactive oxygen and nitrogen species, which lead to oxidative stress and mitochondrial impairment, elements associated with the onset of dementia. Nonetheless, microglia can also assume anti-inflammatory behaviors that facilitate remyelination [54].

Clinical Presentation

Upon presentation of a clinically isolated condition, multiple sclerosis (MS) is frequently presumed. The clinical presentation may be either unilateral or multisymptomatic, contingent upon the lesion's location within the central nervous system (CNS). The most commonly observed manifestations are brainstem involvement, spinal cord syndrome, and optic neuritis; however, rarer presentations, such as cortical disorders comprising dominant parietal lobe syndromes, have also been documented [57]. Multiple sclerosis relapses generally develop subacutely over hours or days, stabilize for several weeks, and subsequently improve progressively. In the initial phases of MS, clinical recovery after a relapse typically seems to be total. Nonetheless, the majority of relapses lead to residual impairment [58]. Visual acuity may improve following a bout of acute optic neuritis; nevertheless, deficits in color vision, contrast sensitivity, and depth perception frequently endure. As neuronal reserve diminishes, recovery from successive relapses becomes increasingly incomplete, and cumulative neuronal losses result in enduring functional impairments [59]. Magnetic resonance imaging (MRI) reveals roughly ten "asymptomatic" lesions for each clinical relapse. A tiny lesion situated in a crucial region is likely to produce significant symptoms. The apparent lesions identified on MRI constitute but a portion of the overall damage; several other lesions exist at the microscopic level, especially within deep and cortical gray matter. Secondary progressive MS generally manifests 10 to 15 years following the onset of relapsing-remitting MS (RRMS), characterized by a gradual shift from episodic relapses to a more insidiously progressive disease trajectory. A distinct transition point between the two stages is absent; relapses transpire amid gradual advancement, ultimately resulting in the predominance of the progressive phase [59]. Cognitive impairment and heightened MRI-detected atrophy in the initial phases of MS indicate that neurodegeneration commences simultaneously with the emergence of clinical symptoms. Primary progressive multiple sclerosis (PPMS), comprising 5 to 15% of patients, is defined by the gradual accumulation of impairment impacting the primary brain systems [57]. The predominant manifestation of PPMS is progressive spastic paraparesis; yet, variations including sensory ataxia, cerebellar ataxia, cognitive deterioration, and significant visual impairment are also extensively recorded. The incidence of patients diagnosed with PPMS has decreased in recent years [57,58].

Diagnosis

The McDonald's criteria are widely utilized in clinical and research contexts for the diagnosis of multiple sclerosis (MS). Nevertheless, due to substantial scientific progress over the previous seven years, these guidelines may no longer represent the most current foundation for diagnosis in clinical practice and research settings [60,61]. Recent assessments of the McDonald criteria indicate a necessity for revisions to align with contemporary understanding [60]. The 2017 version of the McDonald's criteria specifically pertains to patients with a clinically isolated syndrome and delineates the criteria for establishing dissemination in space and time of CNS lesions, underscoring the necessity of excluding alternative explanations for the exhibited symptoms [60,61].

Multiple Sclerosis Diagnosis Based on McDonald's Criteria:

The diagnosis of multiple sclerosis (MS), as defined by the McDonald criteria, necessitates particular clinical and diagnostic evidence. Essential components encompass clinical manifestations, cerebrospinal fluid (CSF) examination, and imaging investigations, including magnetic resonance imaging (MRI). The McDonald criteria necessitate a comprehensive evaluation of episodes and lesions to ascertain the existence

and advancement of the disease. In instances of multiple attacks, clinical evidence of a minimum of two lesions, accompanied by historical documentation of a prior attack, is adequate to substantiate a diagnosis; nevertheless, supplementary evidence is preferable for a more thorough diagnosis. For a solitary attack with clinical evidence of a single lesion, dissemination in space must be validated with MRI or supplementary clinical investigation involving an alternate CNS region. In cases where a patient exhibits a single attack alongside indications of two or more lesions, dissemination in time must be established using MRI, the occurrence of a subsequent attack, or the detection of oligoclonal bands (OCBs) in the cerebrospinal fluid (CSF). In the case of a solitary assault with evidence of a single lesion, space dissemination may be validated using MRI or by seeing a following attack at a distinct CNS location, while time dissemination can be established via MRI or the emergence of an additional attack. Ultimately, insidious neurologic development is deemed diagnostic of multiple sclerosis (MS), characterized by the presence of at least one T2 lesion in brain regions often impacted by MS or two or more T2 spinal cord lesions, accompanied by positive cerebrospinal fluid (CSF) findings [60,61].

Management and Treatment

The management of multiple sclerosis (MS) chiefly entails managing acute episodes, mitigating symptoms, and diminishing the biological activity linked to the condition. Disease-modifying therapies (DMTs) include dimethyl fumarate, interferon-beta, natalizumab, fingolimod, and ocrelizumab are the foundation of multiple sclerosis treatment. Upon diagnosis, prompt beginning of treatment is essential, with short-term aims directed at diminishing MRI lesion activity and long-term objectives centered on averting the emergence of secondary progressive MS. Essential factors post-treatment beginning involve confirming patient compliance with the prescribed regimen and observing for possible drug toxicity [3,62].

Ocrelizumab is a targeted medication that specifically depletes CD20-expressing B cells while maintaining pre-existing humoral immunity and the capacity for B cell regeneration. The depletion of B cells disrupts their migration from peripheral blood to the central nervous system (CNS), reduces the presentation of B cell antigens to T cells, alters the secretion of proinflammatory cytokines by B cells, and impairs the activation and differentiation of plasma blasts that produce immunoglobulins. Ocrelizumab is delivered through intravenous infusion every 24 weeks. Preliminary findings from phase 3 studies indicated a minimal risk for heightened malignancies, including breast cancer; nevertheless, prolonged follow-up has revealed cancer rates consistent with anticipated epidemiological data. Despite the emergence of notable herpes virus infections as a recognized adverse impact, post-marketing studies typically validate the results of clinical trials [63,64]. Ocrelizumab is approved for the management of relapsing forms of multiple sclerosis (RMS) and primary progressive multiple sclerosis (PPMS). The therapy protocol consists of two doses of 300 mg administered biweekly, succeeded by 600 mg every six months. To decrease the risk of infusion responses, patients have to receive premedication with 100 mg of methylprednisolone and an antihistamine 30-60 minutes prior to the infusion and should be monitored for 60 minutes following the infusion [62-64].

Rituximab, an anti-CD20 monoclonal antibody, has demonstrated similar efficacy in the treatment of both RMS and PPMS according to preliminary clinical trials and real-world data, while lacking formal regulatory approval for MS therapy [65,66]. Initially sanctioned in 1997 for cancer treatment, rituximab is additionally employed off-label to address several neurological disorders, such as myasthenia gravis and multiple sclerosis. Multiple dosing regimens have been utilized, with patients often receiving 500 to 1000 mg of rituximab intravenously every 6 to 12 months, frequently after an initial regimen of two doses given two weeks apart [65,66]. Natalizumab, an α4β1 integrin antagonist, obstructs the adherence of lymphocytes to endothelial cells, hence inhibiting their transmigration into the central nervous system. Natalizumab dramatically decreases relapse rates and postpones disease progression in RMS patients compared to placebo or interferon-1a, with these advantages being maintained over the long term in real-world investigations [67]. The therapy is done intravenously once a month.

Highly Effective Disease-Modifying Therapies for MS

The subsequent data delineates various disease-modifying treatments (DMTs) for multiple sclerosis (MS), encompassing their mechanisms of action (MOA), indications, modes of administration, efficacy, adverse effects, and possible medication interactions. Ofatumumab, sanctioned in 2020, is an anti-CD20 monoclonal antibody designated for the treatment of relapse types of multiple sclerosis (RMS) as a primary therapeutic option. It is provided through subcutaneous injection every four weeks. Ofatumumab showed a 54% decrease in the annualized relapse rate (ARR) relative to teriflunomide. Frequent adverse effects encompass injection site responses, nasopharyngitis, cephalalgia, intestinal blockage, and hepatitis. Interactions between tofacitinib and the smallpox and typhoid vaccines have been observed [69-71]. Ocrelizumab, authorized in 2017, is an anti-CD20 monoclonal antibody intended for both relapsing multiple sclerosis (RMS) and primary progressive multiple sclerosis (PPMS) as a first-line treatment. It is delivered through intravenous infusion biannually. In RMS patients, ocrelizumab exhibited a 47% decrease in annualized relapse rate (ARR) relative to interferon beta 1a (IFN β1a), whereas in PPMS patients, it achieved a 24% reduction in confirmed disability progression (CDP) after twelve weeks, compared to placebo. Adverse consequences encompass infusion responses, nasopharyngitis, headache, oral herpes, colitis, hypogammaglobulinemia, neutropenia, and an elevated cancer risk. Ocrelizumab interacts with the smallpox, typhoid, and influenza vaccines [72-75].

Alemtuzumab, sanctioned in 2014, is an anti-CD52 monoclonal antibody designated for relapsing multiple sclerosis as a primary treatment. It is delivered through intravenous infusion once daily. Alemtuzumab has shown a 49-69% reduction in annualized relapse rate (ARR) compared to placebo. The adverse effects including headaches, rash, nausea, fever, thrombocytopenia, hypo- or hyperthyroidism, and encephalitis. It interacts with tofacitinib, siponimod, and ponesimod. Natalizumab, authorized in 2004, is an α4β1 integrin inhibitor utilized as a second-line therapy for relapsing-remitting multiple sclerosis (RRMS). It is delivered through intravenous infusion every four weeks. Natalizumab demonstrated a 68% decrease in annualized relapse rate (ARR) and a 42% reduction in sustained disease progression relative to placebo. Frequent adverse effects encompass exhaustion and allergic responses. Interactions between infliximab and tofacitinib have been documented. Mitoxantrone, authorized in 2000, is a DNA intercalator utilized for rhabdomyosarcoma (RMS) and secondary progressive multiple sclerosis (SPMS) as a second- or third-line treatment. It is provided through intravenous infusion on a monthly or tri-monthly basis. Mitoxantrone has demonstrated a 61% reduction in recurrence rates relative to placebo. Recognized adverse effects encompass cardiomyopathy, hepatotoxicity, and promyelocytic leukemia. Mitoxantrone interacts with valspodar, the typhoid vaccination, and the influenza vaccine.

Moderately Effective Disease-Modifying Therapies for MS

Dimethyl fumarate is recommended for the management of relapsing forms of multiple sclerosis (RMS), including clinical syndrome, relapsing-remitting disease, and secondary progressive disease. This medication is generally well-tolerated, though there exists a risk of progressive multifocal leukoencephalopathy (PML). Most patients who developed PML were found to be lymphopenic; hence, regular monitoring of lymphocyte counts is recommended every 6 to 12 months [7, 84, 85, 86]. Fingolimod, the first oral treatment authorized for RMS, works by inhibiting the exit of lymphocytes from secondary lymphoid organs, thus preventing the infiltration of autoreactive lymphocytes into the central nervous system (CNS). While it is generally well-tolerated, laboratory tests have revealed mild side effects. Patients with a baseline absolute lymphocyte count (ALC) of 952/ml on the day following the first dose are at a higher risk of developing lymphopenia during fingolimod therapy. Additionally, heart block and bradycardia have been observed at the initiation of treatment, necessitating a six-hour observation period for all patients receiving their first dose [87, 88]. Ozanimod, a newly approved selective S1P receptor modulator, has demonstrated both efficacy and safety in treating RMS [89, 90].

Ozanimod, approved in 2020, is a sphingosine 1-phosphate receptor modulator indicated for the treatment of clinically isolated syndrome (CIS), RMS, and active secondary progressive multiple sclerosis (SPMS). It is administered orally once daily, with efficacy demonstrated by a 48% reduction in the annualized relapse

rate (ARR) compared to placebo. Side effects associated with ozanimod include headache, hypotension, and herpes zoster. Known drug interactions include abiraterone, duloxetine, and fluconazole [89-91]. Siponimod, approved in 2019, is another sphingosine 1-phosphate receptor modulator. It is indicated for the treatment of CIS, RMS, and active SPMS as a first-line therapy. Like ozanimod, siponimod is taken orally once daily. It has shown a 21% reduction in confirmed disability progression (CDP) compared to placebo. Common side effects include headache, nasopharyngitis, urinary tract infection, and falls. Drug interactions have been noted with alfuzosin, clozapine, and labetalol [92-94].

Cladribine, also approved in 2019, has an unknown mechanism of action but is used for RMS as a second- or third-line therapy. It is administered orally in two treatment courses lasting 4-5 days over two-week periods. Cladribine has demonstrated a 55-58% reduction in ARR compared to placebo. The medication's side effects include headache, lymphocytopenia, nasopharyngitis, neurotoxicity, and nausea. It is known to interact with smallpox vaccine, typhoid vaccine, and influenza vaccine [95-97]. Dimethyl fumarate, approved in 2013, works as a nuclear factor (erythroid-derived 2)-like two pathway inhibitor and is indicated for RMS as a first-line therapy. It is administered orally twice daily. Dimethyl fumarate has shown a reduction in ARR by 48-53% compared to placebo. Common side effects include flushing, diarrhea, nausea, upper abdominal pain, decreased lymphocyte counts, and elevated liver aminotransferase levels. It also interacts with diroximel fumarate [7, 98, 99]. Fingolimod, approved in 2010, is a sphingosine-1-phosphate inhibitor indicated for RMS as a second-line therapy. It is administered orally once daily. Fingolimod has demonstrated a reduction in ARR by 48-60% compared to placebo. Side effects include bradycardia, atrioventricular conduction block, macular edema, elevated liver enzyme levels, and mild hypertension. It interacts with aripiprazole, esmolol, and other drugs [87, 88].

Modestly Effective Disease-Modifying Therapies for MS

Teriflunomide operates by blocking dihydroorotate dehydrogenase, an enzyme essential for pyrimidine production. Teriflunomide is essential in the treatment of multiple sclerosis (MS) and in avoiding brain atrophy by inhibiting the growth of activated autoreactive lymphocytes. Nevertheless, it has boxed warnings pertaining to hepatotoxicity and teratogenicity. Frequent adverse effects encompass cephalalgia, diarrhea, nausea, alopecia, and elevated hepatic alanine transferase levels. Cholestyramine may be employed to expedite the elimination of teriflunomide from the body if required [102]. Glatiramer acetate, comprising four amino acid-derived polypeptides in acetate salt form, may modulate the equilibrium between proinflammatory and regulatory cytokines, hence affecting the immune response [103]. Glatiramer acetate has demonstrated a moderate reduction in relapse rates and specific indices of disease severity, and is regarded as a viable alternative to interferon in the management of relapsing forms of multiple sclerosis (RMS) [103, 104]. Interferon-β, a recognized therapeutic agent, has been shown to moderately decrease relapse rates and enhance MRI indicators of disease activity, while also postponing the advancement of disability [105]. Common side effects linked to interferon-β encompass flu-like symptoms, mild laboratory abnormalities, and injection site responses in patients undergoing subcutaneous administration [105, 106].

Glatiramer acetate, licensed in 2015, possesses an unidentified mechanism of action and is predominantly utilized as a first-line treatment for relapsing multiple sclerosis (RMS). It is delivered through subcutaneous injection either once daily or three times per week. Clinical trials demonstrate a 29% reduction in the annualized relapse rate (ARR) relative to a placebo. Adverse effects frequently encompass reactions at the injection site. Interactions with tofacitinib have been documented. PeglFN β-1a, branded as Plegridy, received approval in 2014 and is suggested as a first-line treatment for clinically isolated syndrome (CIS) and relapsing multiple sclerosis (RMS). The mechanism of action remains incompletely elucidated. PeglFN β-1a is injected subcutaneously biweekly, and clinical trials indicate a 39% reduction in ARR compared to placebo. Typical adverse effects encompass injection-site erythema, influenza-like symptoms, fever, and headaches [109, 110]. Teriflunomide, sanctioned in 2012, functions as a dihydroorotate dehydrogenase inhibitor and is advised as a first-line therapy for relapsing multiple sclerosis (RMS). Administered orally once daily, clinical studies indicate a reduction in ARR of 32-36% vs to placebo. Common adverse effects

include nasopharyngitis, headache, diarrhea, and elevated alanine aminotransferase levels. Interactions with acyclovir, methotrexate, and simvastatin have been documented.

Interferon β-1a (Rebif), authorized in 2002, is indicated for Clinically Isolated Syndrome (CIS) and Relapsing Multiple Sclerosis (RMS) as a primary treatment. The mechanism of action remains incompletely elucidated. It is delivered through subcutaneous injection thrice weekly, and research indicates a 33% reduction in annualized relapse rate compared to placebo. Frequent adverse effects encompass inflammation at the injection site, flu-like symptoms, rhinitis, and headaches. It engages with zidovudine [113]. Interferon β-1a (Avonex), sanctioned in 1996, is utilized as a first-line treatment for clinically isolated syndrome (CIS) and relapsing multiple sclerosis (RMS). Similar to Rebif, Avonex is administered by injection; however, it is delivered intramuscularly (IM) on a weekly basis. Avonex has demonstrated a 37% decrease in confirmed disability progression (CDP) relative to placebo. Adverse effects encompass influenza-like symptoms, myalgia, fatigue, chills, and pyrexia, and it interacts with zidovudine [105, 114]. Interferon β-1b (Betaseron), authorized in 1993, is indicated for clinically isolated syndrome (CIS) and relapsing multiple sclerosis (RMS) as a primary treatment and is administered through subcutaneous injection bi-daily. It has shown a 31% decrease in ARR vs to the placebo. Adverse consequences encompass lymphopenia, hepatitis, and anaphylaxis [115-117].

Conclusion:

Multiple sclerosis (MS) is a highly complex, immune-mediated disorder of the central nervous system (CNS) that results in progressive demyelination and axonal damage. Although the precise mechanisms behind MS remain incompletely understood, it is widely accepted that a combination of genetic predisposition and environmental factors contribute to its onset. Advances in research have elucidated the involvement of T cells, B cells, and the breakdown of the blood-brain barrier (BBB) in the disease process, while identifying risk factors such as infections, vitamin D deficiency, smoking, and genetic predisposition. Geographic and demographic patterns, such as the higher prevalence of MS in regions farther from the equator, suggest that environmental factors, including vitamin D levels, may significantly influence the incidence of MS. Moreover, genetic studies have identified specific susceptibility genes, with familial clustering indicating a hereditary component. These findings have paved the way for greater understanding of MS's etiology, potentially guiding future therapeutic interventions. The pathophysiology of MS involves both inflammatory and degenerative processes. The inflammatory response, characterized by the activation of autoreactive T cells and the disruption of the BBB, allows immune cells to infiltrate the CNS and attack the myelin sheath. This leads to the formation of demyelinating plaques, particularly in the white matter of the brain and spinal cord. The loss of myelin causes impaired nerve transmission, leading to the hallmark neurological symptoms of MS. Over time, axonal degeneration and neuronal loss contribute to permanent disability. Current diagnostic criteria for MS have improved with the integration of advanced imaging techniques, such as magnetic resonance imaging (MRI), and the detection of biomarkers like oligoclonal bands in cerebrospinal fluid (CSF). These diagnostic tools have enabled earlier and more accurate diagnosis, which is crucial for initiating treatment early in the disease course. Pharmacological management of MS has evolved significantly, with several disease-modifying therapies (DMTs) now available to manage symptoms and slow disease progression. These therapies aim to modulate the immune system, reduce inflammation, and prevent further demyelination. Newer immunomodulatory treatments, including biologics, are showing promise in clinical trials, offering hope for more targeted and effective interventions. However, MS remains clinically untreatable, and the goal of therapy is to manage symptoms and improve quality of life rather than cure the disease. Despite significant progress, challenges remain in the management of MS. The heterogeneity of the disease, with its varying clinical presentations and rates of progression, complicates treatment selection. Personalized approaches, guided by genetic and biomarker data, may hold the key to improving outcomes for MS patients. The continuing development of new therapies, particularly those that target the underlying immunopathological processes, offers hope for more effective management in the future. In conclusion, while the understanding of multiple sclerosis has advanced, further research is essential to unravel its complex pathophysiology and to develop more precise and effective treatments. Improved diagnostic techniques and the emergence of novel therapies provide optimism for better

management of the disease, but ongoing challenges highlight the need for continued efforts in both research and clinical practice. The ultimate goal is to provide personalized care that addresses the diverse manifestations of MS and significantly improves the quality of life for those affected by this debilitating condition.

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التصلب المتعدد :(MS) نظرة عامة، الفيزيولوجيا المرضية، التشخيص، والعلاج الدوائي - مراجعة محدثة

الملخص:

الخلفية: التصلب المتعدد (MS) هو اضطراب مزمن التهابي ناتج عن جهاز المناعة يؤثر على الجهاز العصبي المركزي(CNS) ، مما يؤدي إلى إزالة الميالين والتدهور العصبي. تتضمن الفيزيولوجيا المرضية استهداف جهاز المناعة لغمد الميالين، مما يؤدي إلى مجموعة من الإعاقات العصبية. يتميز التصلب المتعدد بحلقات من الانتكاسات والتحسن، مما يشكل عبئًا كبيرًا على الأفراد والمجتمع. على الرغم من التقدم في فهم التصلب المتعدد، إلا أنه لا يزال حالة صعبة في العلاج.

الهدف: تهدف هذه المراجعة إلى تقديم فهم محدث للتصلب المتعدد، بما في ذلك أسبابه، والفيزيولوجيا المرضية، والتشخيص، والعلاج الدوائي.

الطرق: تم إجراء مراجعة شاملة للأدبيات الحالية المتعلقة بالتصلب المتعدد، مع التركيز على التطورات الحديثة في الفيزيولوجيا المرضية، وعوامل الخطر، والعلاجات الناشئة. تشمل المجالات الرئيسية للبحث العوامل الوراثية والبيئية التي تؤثر على بداية المرض، والتقدم في تقنيات التشخيص، وفعالية العلاجات الدوائية الحالية.

النتائج: يتأثر التصلب المتعدد بمزيج من القابلية الوراثية والعوامل البيئية، مع وجود اختلافات جغرافية وديموغرافية ملحوظة. أدت التطورات الأخيرة في معايير التشخيص، بما في ذلك استخدام المؤشرات الحيوية مثل الأشرطة الأوليغوكلونال، إلى تحسين التشخيص المبكر. تطورت العلاجات الدوائية، مع ظهور العلاجات المناعية الجديدة التي تظهر وعودًا في التجارب السريرية. ومع ذلك، لا يزال التصلب المتعدد صعب العلاج، ولا يوجد علاج حاسم.

الخلاصة: التصلب المتعدد هو مرض مناعي معقد مع تباين كبير في تقديمه وتقدمه. هناك حاجة إلى مزيد من البحث لفهم فيزيولوجية المرضية بشكل أفضل ولتطوير علاجات أكثر فعالية وشخصية. تشكل الأساليب التشخيصية المحسنة والعلاجات الدوائية الجديدة وعودًا بتحقيق إدارة أفضل، على الرغم من أن التحديات ما زالت قائمة في تقديم الرعاية المثلى.

الكلمات المفتاحية: التصلب المتعدد، الفيزيولوجيا المرضية، التشخيص، العلاج الدوائي، مرض مناعي، إزالة الميالين، جهاز المناعة.