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Decoding Multiple Sclerosis: Insights into Subtypes, Mechanisms, and Advancing Treatments

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ABSTRACT

Multiple sclerosis (MS) is a complex and common neurological disorder that affects the central nervous system. The disorder is characterized by severe symptoms such as weakness, fatigue, cognitive impairments, and spasticity, which all significantly impact the quality of life for those with a diagnosis. A hallmark of multiple sclerosis is the autoimmune attack against myelin sheaths, resulting in demyelination. Unfortunately, there is no cure for MS. A need exists to understand more about MS due to its substantial and rising burden on patients, families, and health systems. Early diagnosis and intervention are critical to mitigating irreversible damage and improving outcomes. This review highlights the pathophysiological mechanisms driving the disease and the current advancements in treatments such as insights into immune endophenotypes and novel biomarkers which may revolutionize MS care in the future.

Introduction

Multiple Sclerosis is one of the most common neurological disorders, having a prevalence of 570,000 patients [1]. Multiple sclerosis affects the central nervous system (CNS) which is composed of the brain, spinal cord, and optic nerves. The disease manifests with a range of diverse symptoms, including weakness, reduced cardiovascular fitness, ataxia (lack of muscle coordination), fatigue, bladder dysfunction, pain, cognitive deficits, and spasticity, which is characterized by increased muscle tone leading to stiffness and involuntary muscle contractions (Figure 1). It is female-predominant and highly variable in geographic distribution [2]. The average onset for the disease is 30 years old which poses a large socioeconomic and personal burden to patients and their families [3].

There are 3 subtypes of MS that differ by the progression of the disease and symptoms: relapsing-remitting, secondary remission, and primary progressive MS [4]. Remitting-relapsing multiple sclerosis (RRMS) is the most common type of MS and is characterized by episodes of neurological symptoms (relapses) followed by periods of partial or complete recovery (remissions) (Figure 2) [5]. Following RRMS, many patients progress into the subtype of MS known as secondary-remitting MS. Although a standardized objective definition of SPMS has not been broadly accepted, it is typically defined as deterioration independent of relapses for ≥6 months following an initial relapsing-remitting course [6]. Primary progressive affects about 10% of patients and is characterized by slow accumulation of neurological disability without relapses [7].

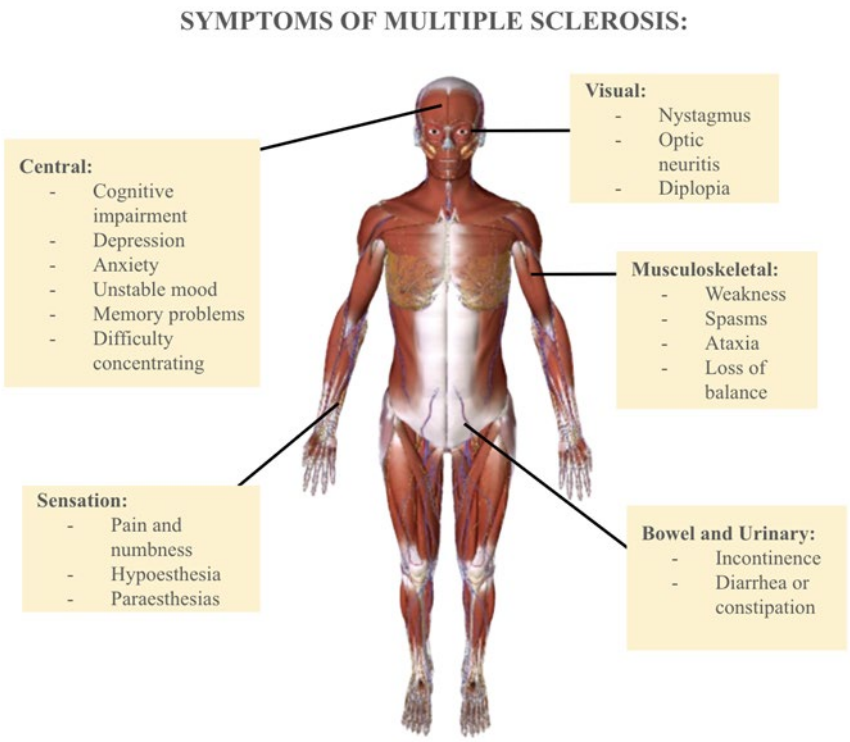

Figure 1. Clinical manifestations of MS. Major organ systems affected include the brain, peripheral nervous system and musculoskeletal system.

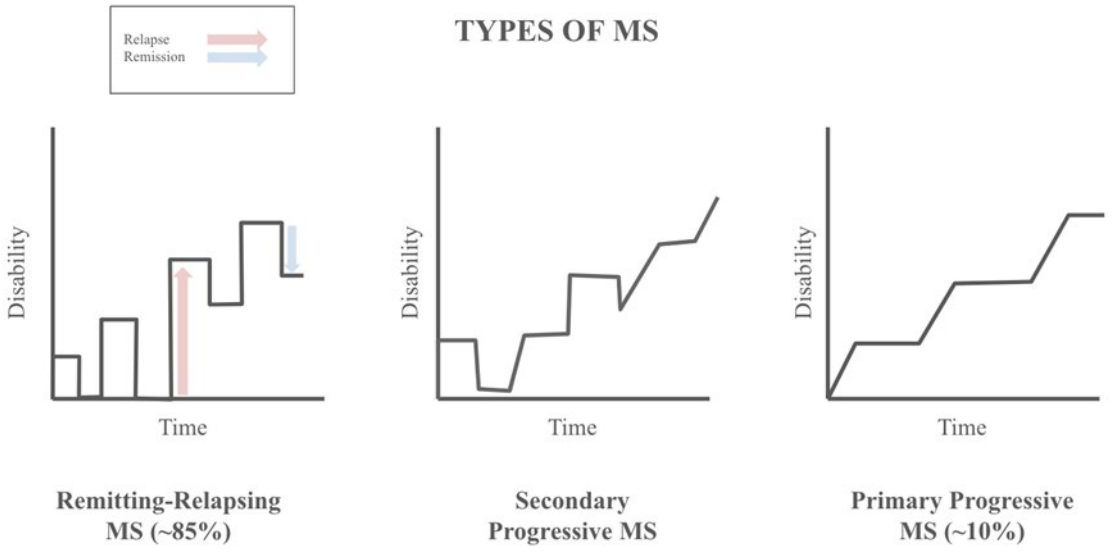

Figure 2. Subtypes of MS. Progression of disability in Remitting-Relapsing MS, Secondary Progressive MS, and Primary Progressive MS

There is no cure for multiple sclerosis. Treatment typically focuses on speeding recovery from attacks, reducing new radiographic and clinical relapses, slowing the progression of the disease, and managing MS symptoms [8]. While immunotherapies are being tested, they are not the standard of care for patients yet.

The main process that drives the progression of Multiple Sclerosis is when the autoimmune system mistakenly attacks the protective covering of the nerve fibers, myelin sheath, which results in inflammation [9]. Demyelination is a key process in Multiple Sclerosis and substances like myelin basic proteins (MBP), proteolipid protein, and myelin oligodendrocyte glycoprotein (MOG) are thought to be the main targets of the autoimmune response (Figure 3) [10].

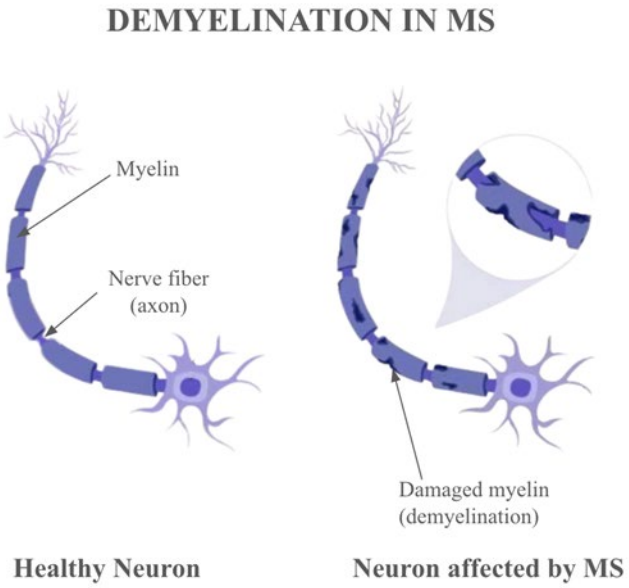

Figure 3. Demyelination in MS. Comparison of a Healthy Neuron and Neuron affected by MS

The exact cause of MS is unknown but it arises in genetically susceptible individuals, random events, and due to environmental factors. For instance, MS risk modulators, including genetic variants in interleukin-7 receptor-α (*IL7RA**C), interleukin-2 receptor-α (*IL2RA**T), *MGAT1* (IVAVT−T) and *CTLA-4* (Thr17Ala), and environmental factors affecting vitamin D3 levels, converge in order to alter branching of Asn (N)-linked glycans [11]. It's also uncertain whether MS is triggered in the periphery or CNS. The two current hypotheses are that autoreactive T cells, self-attaching cells, are activated at peripheral sites. They traffic to the central nervous system with activated B cells and monocytes. The other hypothesis is that the infiltration of autoreactive lymphocytes occurs as a secondary phenomenon to an unknown viral infection in the CNS [12]. This paper will discuss the pathophysiology of the major immune cells involved in MS and highlight current treatments under development for the subtypes of Multiple Sclerosis.

Relapsing-Remitting MS

Patients with MS can have various clinical courses, but the most common pattern seen is relapsing-remitting multiple sclerosis (RRMS). It is the most prevalent form, affecting 85% of individuals [13]. In RRMS, people have distinct attacks of symptoms which then fade away either partially or completely. Symptoms may not all be experienced simultaneously but can include visual disturbance, lack of balance and dizziness, chronic fatigue, bladder

incontinence, pain, muscle weakness or spasticity and cognitive impairment [14]. RRMS can be categorized into two forms: Highly Active Relapsing Remitting Multiple Sclerosis (HARRMS) and Rapidly evolving severe (RES). European Medicines Agency (EMA) defines patients with HARRMS as treatment naïve patients with at least two disabling relapses in the last 1 year and concurrent MRI imaging with at least one gadolinium-enhancing lesion or significant increase in T2-lesion load [15].

The pathophysiology of RRMS involves an autoimmune response targeting the myelin sheath of nerve fibers in the central nervous system, leading to demyelination and axonal damage [16]. This disrupts nerve signal transmission, causing neurological symptoms. It is crucial that patients experiencing RRMS be treated with early initiation of effective immunotherapy due to a narrow therapeutic window for anti-inflammatory agents. The National MS Society has identified more than 136 studies to evaluate the different therapeutic options for MS with the oldest being interferon beta, either used alone or as add-on therapy with other drugs [17]. The most common treatments are glucocorticoids which are used to reduce nerve inflammation. Glucocorticoids are used to down-regulate expression levels of pro-inflammatory cytokines and adhesion molecules required for leukocytes to pass through the blood-brain barrier (BBB) [18]. They also promote apoptosis (cell death) in immune cells, inhibit T cell activation, and additionally exert further anti-inflammatory effects [18]. These therapeutic options underscore the importance of early and targeted treatment to manage RRMS effectively to improve patient outcomes [19].

Secondary Progressive Multiple Sclerosis

Multiple sclerosis (MS) often begins as relapsing-remitting MS (RRMS) but can progress to secondary progressive MS (SPMS) [6]. It is hypothesized that MS initially manifests as an inflammatory disease (RRMS) and later evolves into a neurodegenerative condition independent of inflammatory responses (SPMS) [20]. Without treatment, approximately half of individuals with relapsing-remitting multiple sclerosis (RRMS) convert to secondary-progressive multiple sclerosis (SPMS) within 10 years [21]. This transition underscores the need to understand the underlying pathology of this progression and improve treatments for SPMS.

Diagnosing SPMS presents challenges due to the absence of a universally accepted diagnostic criteria, the heterogeneous nature of the disease, indistinct clinical features of progression, and a lack of definitive imaging or biomarkers that distinguish RRMS from SPMS [22]. Progression in early RRMS can be gradual and unnoticed, a phenomenon known as “silent progression” [23]. Patients and physicians often fail to detect SPMS in its early stages because the brain compensates for neuronal loss through mechanisms such as increased neuronal recruitment, activation of additional brain areas, and local neuronal plasticity [24]. This compensation can lead to a "transition period" between RRMS and SPMS, resulting in diagnostic uncertainty and potential treatment delays.

SPMS is typically defined as a phase where patients experience continuous deterioration independent of relapses for at least six months following an initial relapsing-remitting course [6]. Symptoms of SPMS, such as fatigue, reduced mobility, and increased disability, are often exacerbated by physical activities like walking long distances, climbing stairs, or carrying heavy objects [6]. These symptoms can be particularly challenging for patients to manage and significantly impact their quality of life.

MRI studies have shown that focal white matter lesions on MRI imaging are less common in patients with primary progressive MS compared to those with SPMS [25]. However, tertiary lymphoid follicles (clusters of immune cells) in the meninges are more frequently observed in SPMS cases, suggesting a distinct pathological feature of this stage [26]. Additionally, gray matter atrophy and cortical lesions become more prominent as the disease progresses to SPMS, highlighting the neurodegenerative aspect of this subtype [Emerging research aims to better understand the biological mechanisms underlying the transition from RRMS to SPMS, which is critical for developing targeted therapies to slow or prevent this progression. Advancements in imaging techniques and the identification of novel biomarkers could improve early diagnosis and intervention strategies, ultimately enhancing the quality of life and clinical outcomes for patients with SPMS.

Primary Progressive Multiple Sclerosis

Primary Progressive Multiple Sclerosis (PPMS) is one of the most challenging and least understood forms of MS, affecting 10-15% of all MS patients. It is characterized by a steady progression of neurological decline without the distinct relapses and remissions, which is often seen in other MS types [27]. PPMS is difficult to discern at the onset of neurological symptoms because it often requires several visits to a physician to establish the continuous worsening over time [28]. Other challenges in distinguishing PPMS from SPMS is the lack of qualitative differences in the disease activity, lesion morphology or immunopathology. In addition, there are no biomarkers that differentiate SPMS from PPMS [28]. However, PPMS can be distinguished from other forms of MS due to the lack of relapses [29]. Spinal cord lesions are more common than brain lesions in PPMS, so problems with walking are very commonly seen in PPMS patients. Other common symptoms seen in PPMS are balance problems, bladder and bowel issues, muscle weakness, paralysis, and tremors [29].

The treatment options for patients with progressive forms of MS are generally limited, although the recent availability of novel treatments has expanded the disease-modifying treatment (DMT) options for these MS phenotypes [30]. One clinical trial investigated the potential of high-dose biotin, which is a form of vitamin B, to reverse the disability in patients diagnosed with PPMS. Biotin reverses disability through increasing the production of energy to help the demyelinated neurons from being damaged. The primary efficacy endpoint, or outcome, was disability reversal at month 9, which was confirmed at month 12. Disability reversal was defined as a decrease in EDSS (Expanded Disability Status Scale) of ≥1 for patients with a baseline of EDSS <6. Overall, 13 patients in the biotin group (12.6%) and none in the placebo group achieved the sustained disability reversal endpoint ($p = 0.005$) (in text citation needed here). However, another study followed similar procedures but did not obtain the primary efficacy endpoint. Other complementary therapies to treat PPMS include occupational therapy, physical therapy, speech language-pathology, and exercise [31].

Possible Treatments

While there isn't any cure for MS, research has been ongoing to find better disease modifying treatments (DMTs) to reduce the severity of the attacks. Some treatments that have been FDA approved for RRMS and SPMS are Ublituximab-xiiy (Briumvi), Ofatumumab (Kesimpta), Siponimod (Mayzent), and Cladribine (Mavenclad) [32]. Briumvi was approved in 2022 and is an anti-CD20 antibody that prevents B cells from making antibodies that could damage the brain and spinal cord. Kesimpta, approved in 2020, works similarly to Briumvi to deplete B cells. Mayzent is an oral medication that prevents lymphocytes (T- and B-cells) from leaving the lymph nodes through blocking S1PR. Mavenclad is an oral medication that reduces relapse rates in patients that cannot take other medications approved for MS. Its mechanism of action is not fully understood but it suppresses lymphocyte function.

Most current treatment options for patients with MS are based on a combination of factors: clinical and subclinical parameters of disease activity and severity, safety aspects, and patient preferences. However, this approach is not the most effective way to treat patients due to the heterogeneity of the underlying immune dysregulation [33].

In an effort to bridge this gap in treatment, one study found that the immune signatures of MS patients split into three distinct immunological endophenotypes [34]. Endophenotypes are quantifiable phenomena that are distinct from symptoms and link genes to manifest illness [35]. This study used standardized, clinical data collected from a comprehensive cohort of more than 1,200 therapy-naïve patients with early (≤2 years from disease onset) MS (NationMS cohort). Then, they analyzed peripheral blood mononuclear cells (PBMCs) and serum collected from a subcohort of 309 patients with early RRMS. These samples were subjected to a high-dimensional characterization of peripheral immune signatures by combining multiparameter flow cytometry and targeted proteomics. Existence of these three immunological endophenotypes was confirmed in an independent validation cohort of 232 patients with MS. One of these found endophenotypes termed the "degenerative" endophenotype was associated with increased

signs of early structural damage and disability progression, whereas the "inflammatory" endophenotype was associated with increased signs of high inflammatory disease activity. Standard immune therapies for MS differed in their capacity to reverse immune signature alterations associated with each endophenotype.

The symptoms that the patients exhibited also greatly differed. Patients classified under the E1 endophenotype of early multiple sclerosis (MS) exhibited symptoms predominantly associated with early structural damage, including higher clinical disability at baseline, early cognitive deficits, elevated serum neurofilament light chain (sNfL) levels, and increased intrathecal IgM synthesis. These patients showed a marked presence of T cells producing TH17 cytokines like IL-17A, IL-22, and GM-CSF, which are known for their destructive effects on brain endothelial cells and resident cells. Conversely, patients in the E3 endophenotype demonstrated a higher degree of inflammatory activity, characterized by inflammatory cerebrospinal fluid (CSF) alterations, high relapse frequency, presence of gadolinium-enhancing lesions, and early necessity for high-efficacy treatments. These patients had significant disturbances in the CD8 T cell compartment and often required early escalation to more potent disease-modifying therapies (DMTs) such as glatiramer acetate (GA) and dimethyl fumarate (DMF). Notably, interferon-beta (IFN-β) showed a reduced capacity to correct immune alterations in E3 patients and was associated with increased clinical and MRI progression, suggesting that GA and DMF might be more effective treatment options for managing the inflammatory activity in this subgroup. For patients with RRMS, DMF is administered orally in capsule form, with an initial dose of 120 mg taken twice daily for the first 7 days, followed by a maintenance dose of 240 mg taken twice daily. Common side effects when taking DMF include flushing, gastrointestinal issues (nausea, diarrhea, abdominal pain, vomiting), increased risk of upper respiratory tract infections [36]. Therefore, monitoring is needed to ensure the patient's therapy with DMF.

Conclusion

MS remains a complex neurological disorder that requires additional research to understand underlying pathogenesis and subsequent clinical manifestations to inform the development of more targeted and effective therapies. Current treatments predominantly focus on symptoms management and immune modulation, yet they fall short of providing a cure or significantly altering disease progression for all patients. However, the recent identification of distinct immune endophenotypes offers promising avenues for personalized medicine and effective therapeutic strategies. For patients with early RRMS, determination of endophenotypes through routine blood work has emerged as an important clinical biomarker. The future of MS research will rely heavily on the integration of advanced imaging techniques, novel biomarkers, and a deeper understanding of the disease's pathophysiology in order to improve patient outcomes.

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