REVIEW ARTICLE

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Multiple Sclerosis: A Comprehensive Review of Pathophysiology, Clinical Manifestations, Diagnosis, Treatment, and Future Perspectives

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Abstract

Multiple Sclerosis (MS) is a chronic autoimmune disorder of the central nervous system with an increasing global prevalence. Its etiology involves a complex interaction between genetic susceptibility and environmental factors. This review examines the pathophysiology of MS, focusing on the immune-mediated demyelination and neurodegeneration that drive disease progression. We summarize the diverse clinical manifestations of the disease, from common sensory-motor deficits to less typical presentations. Diagnostic approaches are discussed, including the application of the 2017 McDonald Criteria and the roles of neuroimaging, cerebrospinal fluid analysis, and evoked potentials. We also highlight the emerging use of artificial intelligence in improving diagnostic accuracy and prognosis. The current landscape of disease-modifying therapies is outlined, covering established treatments for relapsing MS and addressing the unmet need for effective therapies for progressive forms of the disease. Finally, we discuss future perspectives in MS treatment, including stem cell therapies and novel biomedical engineering strategies aimed at promoting remyelination. This review synthesizes current knowledge to provide a comprehensive overview of the path from diagnosis to emerging therapeutic frontiers in Multiple Sclerosis.

Keywords: Multiple Sclerosis, Autoimmune Disease, Disease-Modifying Therapies, Artificial Intelligence, Stem Cells.

1. Introduction

Autoimmune diseases (ADs) represent a diverse group of conditions where the body's immune system continually attacks its own cells and tissues, a phenomenon termed autoimmunity. This broad category encompasses over 100 distinct diseases, including several examples such as type 1 diabetes mellitus, rheumatoid arthritis, systemic lupus erythematosus, and multiple sclerosis [1-5]. ADs are typically categorized as either organ-specific (OS), where the immune response is directed against antigens within a single organ, or non-organ-specific (NOS), involving systemic immune attack across multiple systems. Multiple sclerosis (MS) is an example of an NOS autoimmune disease, specifically targeting the central nervous system (CNS) [6-9].

Multiple sclerosis is a chronic, demyelinating, and inflammatory disease primarily affecting the brain and spinal cord [16-18]. Demyelination, the hallmark of MS, involves the inappropriate immune-mediated destruction of myelin, the fatty sheath that insulates nerve fibers. This damage disrupts efficient neuronal communication, leading to a wide spectrum of sensory, motor, and cognitive impairments [19]. Globally, MS is recognized as the most prevalent chronic inflammatory disease of the CNS, affecting over 2.8 million individuals worldwide [10]. The disease exhibits a notable sex disparity, with the majority of diagnoses occurring in women [11]. While the precise reasons for this are not fully understood, contributing factors may include sex-specific epigenetic modifications, significant hormonal fluctuations during puberty, and environmental influences such as varying sun exposure [12].

The etiology of MS is complex, arising from intricate interactions between genetic predisposition and environmental exposures [13]. Key environmental factors contributing in MS risk include sunlight exposure, vitamin D levels, dietary habits, early-life

obesity, smoking, and infections with agents like Epstein-Barr virus (EBV), human herpesvirus-6 (HHV-6), and human endogenous retroviruses [14, 15]. These exposures may contribute to the observed increase in MS incidence year by year. Despite the global prevalence of MS, the exact primary risk factors remain incompletely understood. Furthermore, the absence of a definitive cure underscores the urgent and ongoing need for continued research to discover more advanced and effective treatment options. MS represents a serious and potentially disabling autoimmune disorder that profoundly impacts the quality of life of affected individuals, characterized by its chronic nature and progressive neurological symptoms.

This comprehensive review aims to provide a detailed overview of multiple sclerosis, focusing on five critical domains essential for understanding and managing the disease: its pathophysiology, clinical manifestations, diagnostic approaches, current treatment options, and future perspectives. By systematically examining these areas, we highlight the multifaceted complexity of MS and the persistent global efforts dedicated to improving outcomes for those living with this challenging condition.

2. Pathophysiology of Multiple Sclerosis

Multiple sclerosis is characterized by a progressive neuropathological process involving inflammation and nerve damage within the CNS, which can ultimately lead to permanent neurological disability [20]. The disease's impact can be profound, with symptoms such as tremors significantly affecting daily life, potentially leading to early retirement or unemployment [21]. Timely recognition of MS as a cause of new tremor symptoms is crucial to avoid delays in diagnosis and the initiation of appropriate therapy [21].

The pathogenesis of MS involves a complex interplay of immune cells and glial cells within the CNS. While interactions between astrocytes and microglia can exacerbate neuroinflammation in various brain diseases, they also play a crucial role in mitigating CNS damage. For instance, microglia-derived Interleukin-10 (IL-10) can induce astrocytes to release transforming growth factor beta (TGF-β), which in turn helps suppress microglial inflammation [22]. A central event in MS is the aberrant activation of T lymphocytes, which become self-reactive upon encountering an unknown autoantigen presented by major histocompatibility complex (MHC) class II molecules [23, 24]. These autoreactive T cells then migrate to peripheral lymphoid organs, where they proliferate. Following activation by sphingosine-1-phosphate (S1P), these activated T cells circulate in the bloodstream. Upon stimulation, they adhere to overexpressed adhesion molecules on the endothelial lining of blood vessels and secrete Matrix Metalloproteinases (MMPs), enzymes that degrade components of the extracellular matrix. This enzymatic activity facilitates the breach of the blood-brain barrier (BBB), allowing immune cells to infiltrate the CNS [24]. Within the CNS, these infiltrating immune cells contribute to the pathological process by producing a diverse array of cytokines, including both pro-inflammatory and anti-inflammatory mediators [25]. While MS commonly manifests in individuals aged 20 to 40 years, it can develop at any age. The average age of onset for relapsing-remitting MS (RRMS) is typically 25 to 29 years, whereas primary progressive MS (PPMS) generally presents later, between 39 to 41 years [26]. Certain infections, particularly EBV, are thought to influence disease onset [27].

The spatial distribution of spinal cord lesions varies across MS subtypes. The dorsal column is frequently affected in all forms, while the lateral funiculi are more commonly impacted in primary and secondary progressive MS compared to the relapsing-remitting form [28]. Cervical spinal cord atrophy serves as a significant indicator of disease progression, often predicting the transition to secondary progressive MS (SPMS) even in the absence of overt clinical relapses or other active disease symptoms [29].

Experimental autoimmune encephalomyelitis (EAE) is the most widely utilized animal model for MS. This model is characterized by an adaptive immune response where myelin-reactive T cells infiltrate the CNS, leading to autoimmune demyelination and axonal destruction [30]. The progression of MS pathophysiology, from immune activation to chronic axonal damage, is schematically represented in Figure 1.

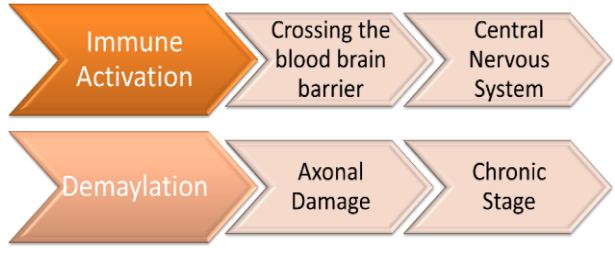

Figure 1. Progression of Multiple Sclerosis Pathophysiology.

The clinical presentation of MS can be highly variable due to individual patient factors, including age, sex, genetic background, environmental exposures, and disease duration [31]. Furthermore, the senescence of different CNS cell subtypes, which can be accelerated by the disease process itself, may influence disease progression. In senescent microglia, reduced phagocytic activity can lead to persistent inflammatory cytokine release and hinder remyelination. Similarly, senescent astrocytes can impair synaptic plasticity, disrupt BBB function, and disturb the metabolic stability of adjacent neurons [32]. Cytokines and chemokines found in the cerebrospinal fluid (CSF) primarily originate from

meningeal infiltrates. Their distribution correlates with the presence and size of cortical lesions, the degree of neurodegeneration in the cortex, and the release of neurofilament light chain (NfL) protein, a recognized biomarker of neurodegeneration [33].

3. Clinical Manifestations of MS

Multiple sclerosis presents with a broad array of symptoms reflecting the widespread nature of CNS lesions. The diversity and intensity of these symptoms are directly influenced by the quantity, specific location, and severity of tissue damage [34]. Interestingly, clinical symptoms may not always correlate directly with MRI evidence of active plaques, highlighting the role of repair mechanisms and brain plasticity in tissue injury and recovery processes [34].

Typical clinical manifestations frequently noted in patient history include:

• Visual problems: Common symptoms involve visual loss (either monocular or homonymous), diplopia (double vision), pain with eye movement, and signs characteristic of optic neuritis [34].

• Vestibular symptoms: Imbalanced gait and vertigo are also frequently observed [34].

• Bulbar dysfunction: Dysarthria (slurred speech) and dysphagia (difficulty swallowing) may occur, indicating involvement of the lower cranial nerves [34].

• Motor symptoms: Prominent motor deficits often include debilitating fatigue, tremors, spasticity, and varying degrees of weakness, such as hemiparesis (weakness on one side of the body), monoparesis (weakness in one limb), or paraparesis (weakness in both legs) [35-37].

• Sensory disturbances: These are typical and may present as a band-like sensation around the chest or abdomen (MS hug), paresthesia (tingling or prickling sensation), dysesthesias (unpleasant abnormal sensations), or numbness [36].

• Autonomic dysfunction: Commonly affects the digestive and urinary systems, leading to symptoms like gastroesophageal reflux, diarrhea, constipation, urinary urgency, retention, or incontinence [35, 36].

• Cognitive issues: Difficulties with concentration, memory impairment, and problems with executive functions are frequently reported [35].

• Psychiatric manifestations: Depression and anxiety often coexist with MS and can significantly impact quality of life [35].

• Brainstem involvement: Can result in symptoms such as diplopia, oscillopsia (illusory movement of visual field), facial muscle weakness, and reduced facial sensation [35]. The primary clinical manifestations of MS are further illustrated in Figure 2.

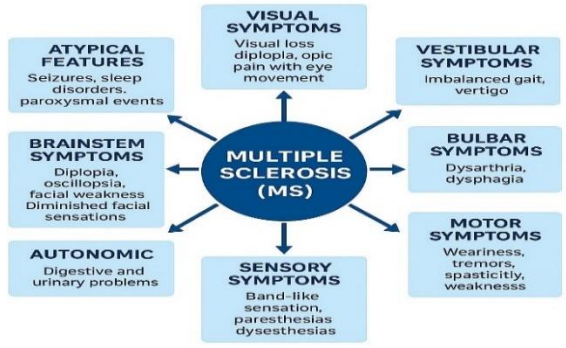

Figure 2. The main clinical manifestations of multiple sclerosis.

4. Atypical Features Warranting Further Evaluation in Suspected MS

Certain clinical features are considered atypical for MS and should prompt careful consideration of alternative diagnoses [36, 38]. These include:

• The presence of seizures.

• A steadily progressive course without relapses from onset (unless primary progressive MS is being considered, but typically atypical for typical RRMS).

• Symptoms that develop abruptly within minutes.

• Disease onset before the age of 10 or after 50.

• Movement abnormalities such as rigidity or sustained dystonia.

• Cortical signs like apraxia, alexia, aphasia, or neglect.

• Early-onset dementia [36].

Most MS patients experience a RRMS, characterized by episodic neurological exacerbations (relapses) followed by periods of partial or complete recovery. During the recovery phases, the disease remains clinically stable [36]. Relapses in RRMS typically involve the gradual development of new or recurrent neurological symptoms over several days to weeks, usually lasting between 24 and 48 hours, and often showing partial or complete resolution. However, with repeated relapses over time, patients may accumulate residual neurological deficits, leading to long-term disability [37]. This progression often becomes more apparent after 10 to 15 years of disease onset, at which point many patients transition to a secondary progressive course (SPMS), marked by a steady worsening of symptoms with or without ongoing relapses. The neurological manifestations in RRMS vary widely in terms of severity and the degree of recovery following each episode [37].

Other atypical features that warrant further evaluation in suspected MS include [38]:

• Seizures and Sleep Disorders: Such as obstructive sleep apnea, nocturia, insomnia, and restless legs syndrome [39].

• Transient or Paroxysmal Neurological Events: These are brief, often lasting only seconds, and can occur with variable frequency. They include:

• Abnormal or unexplained sensations spreading across the body.

• Brainstem-related manifestations like blurred vision, diplopia, dysarthria, and vertigo.

• Motor disturbances such as transient inhibition of motor function, tonic spasms, or ataxia.
• Rarely, gustatory symptoms (taste hallucinations or altered taste perception) or thermoregulatory issues (hypothermia or hyperthermia) [39].
• Visual Disturbances: May present as the Pulfrich phenomenon (arising from a mismatch in visual acuity between the eyes, causing objects moving in a straight line to appear to follow an elliptical path). These visual abnormalities can lead to practical difficulties in daily activities [39].
• Distinctive but Uncommon Symptoms:
• The "useless hand of Oppenheim," where the patient experiences a sudden loss of function in the hand.
• The Lhermitte phenomenon, particularly when triggered by less typical actions such as limb movements, neck extension, or coughing [39].

5. Diagnosis of MS

The diagnosis of MS relies on an integrated assessment of clinical presentation, neuroimaging findings, and laboratory results [40]. While no single test is definitively diagnostic [41], various diagnostic criteria have been developed to synthesize clinical observations with supportive ancillary data, facilitating accurate disease identification [42]. The most widely utilized diagnostic framework is the McDonald Criteria.

I. The 2017 McDonald Criteria: Originally introduced in 2001 and subsequently revised in 2005, the McDonald Criteria underwent its most recent update in 2017, as presented in Table 1 [40, 42]. The 2017 revision refined diagnostic principles by eliminating the distinction between symptomatic and asymptomatic lesions and by re-categorizing juxtacortical involvement, merging cortical and juxtacortical lesions. This broadened the scope of lesion localization within the central nervous system. The fundamental principle of these criteria is the demonstration of dissemination in time (DIT) and dissemination in space (DIS), evidenced through clinical manifestations and/or magnetic resonance imaging (MRI) findings [40].

II. Magnetic Resonance Imaging (MRI): The advent of MRI in the early 1980s revolutionized the diagnostic and therapeutic landscape of MS, providing unparalleled in vivo visualization of lesion activity and disease burden. Through continuous technological advancements over the subsequent decades, MRI has evolved into the most essential paraclinical modality for both the initial diagnosis and ongoing monitoring of MS [43]. MRI plays a pivotal role in MS diagnosis, with current International Panel on MS Diagnosis criteria allowing for disease confirmation based on findings from a single time-point MRI scan [42].
MRI techniques used in the evaluation of MS are broadly classified into two main categories: conventional and advanced.

Table 1. 2017 McDonald Criteria for Diagnosis of Relapsing-Remitting MS (RRMS)

Number of Clinical Attacks	Number of Lesions with Clinical Evidence	Additional Evidence Required for MS Diagnosis
2 or more	Lesions in 2 or more CNS locations	No additional information needed. Diagnosis confirmed.
2 or more	Lesion in only 1 CNS location	No additional information needed. Diagnosis confirmed.
2 or more	No MRI lesions, only one CNS site involved	Need proof of dissemination in space (DIS) via another clinical attack affecting a different CNS site or by MRI evidence.
1	Lesions in 2 or more CNS locations	Need proof of dissemination in time (DIT) via a second attack, MRI findings of new lesion(s), or positive CSF-specific oligoclonal bands.
1	Lesion in only 1 CNS location	Must demonstrate both: DIS (via another attack or MRI showing different CNS region), and DIT (via new clinical attack, MRI, or CSF oligoclonal bands).

• Conventional MRI encompasses widely accessible, well-established, and highly standardized imaging protocols, first integrated into the diagnostic framework with the original International Panel guidelines [44]. These protocols typically include T2-weighted, fluid-attenuated inversion recovery (FLAIR), short-tau inversion recovery (STIR), and T1-weighted sequences acquired before and after gadolinium contrast administration. These are usually performed at magnetic field strengths of 1.5 Tesla in both the brain and spinal cord and remain central to routine clinical assessment and decision-making in MS.
• Advanced MRI techniques, particularly those conducted at higher magnetic field strengths such as 3T and 7T, offer superior signal-to-noise ratios and markedly improved spatial resolution (reaching scales as fine as 100 μm). However, these benefits are accompanied by limitations including greater susceptibility to imaging artifacts, limited protocol standardization across institutions, and higher operational costs [45]. A variety of specialized MRI pulse sequences, such as magnetization transfer imaging (MT), magnetic resonance spectroscopy (MRS), diffusion-weighted imaging, and the use of emerging

contrast agents, have also been employed to enhance diagnostic specificity in MS [46].

III. Spinal Fluid Analysis: The primary advantage of utilizing CSF rather than blood for biomarker measurement in MS is its superior ability to more precisely reflect the inflammatory profile of the CNS [47]. CSF biomarkers offer greater sensitivity than clinical evaluations or MRI scans, particularly when assessing low-grade disease activity in MS. In certain patients whose disease was considered inactive based on clinical scales and/or MRI, levels of CSF NfL and the immunoglobulin G (IgG) index were notably elevated [48].

The IgG index is a ratio that compares the levels of IgG to albumin in the CSF with those in the serum [49]. A ratio greater than 0.7 typically supports a diagnosis of MS. While analyzing CSF for inflammatory markers, such as oligoclonal bands (OCBs) and the IgG index, is useful in diagnosis, these markers are not optimal for predicting relapse and disease progression [50]. The sensitivity of oligoclonal bands can be limited due to difficulties in determining the number of bands present, and their specificity is low as any condition causing chronic CNS inflammation can lead to their increase [50]. However, several studies indicate that IgM-type oligoclonal bands are linked to heightened disease activity in MS, increased retinal axonal loss, reduced retinal nerve fiber layer thickness, and more aggressive disease progression during the early stages of RRMS [49, 51, 52, 53, 54].

IV. Evoked Potentials: Evoked potentials (EPs), including visual evoked potentials (VEPs), somatosensory evoked potentials (SSEPs), and brainstem auditory evoked responses (BAERs), are non-invasive methods used to evaluate neural conduction across various sensory pathways [55]. These tests involve stimulating the respective sensory system, with a scalp electrode placed over the corresponding cortical area to measure latency and amplitude. Prolonged latency is indicative of demyelination-induced damage, making EPs a valuable tool for diagnosing MS and assessing specific neural pathways [55]. Additionally, EPs have a proposed role in predicting MS prognosis and monitoring treatment response, though their widespread clinical application in this context is still developing [56].

V. Kappa Free Light Chain (KFLC): Kappa free light chains (KFLC) are generated during antibody synthesis by plasma cells [53]. CSF Kappa free light chains have been suggested as an additional diagnostic marker for MS, offering similar sensitivity and specificity to oligoclonal bands [57]. Unlike OCBs, KFLC measurements do not require a paired serum sample and provide rapid, machine-operated results, eliminating the need for visual assessment [57]. Specifically, KFLC levels have been found to be elevated in both the CSF and serum of patients with MS [58], and have been associated with future disability progression [59]. Higher CSF levels of KFLC in patients with clinically isolated syndrome (CIS) have also been linked to an earlier conversion to clinically defined MS [60].

VI. The Contribution of AI in Diagnosis: Recent advancements in technology and the increasing availability of large-scale data have facilitated the integration of artificial intelligence (AI) algorithms into the diagnostic work-up of MS [61]. Convolutional neural networks (CNNs), a form of deep learning (DL) capable of automatically extracting relevant features, have successfully distinguished between MS patients and healthy controls (HC) with high accuracy (ranging from 70.2% to 98.8%) based on various MRI sequences, including T2-weighted [62, 63], FLAIR [64], and susceptibility-weighted MRI [65]. Machine learning (ML) algorithms, designed to learn from predefined data features to make decisions or predictions, have also shown promising results. When trained on quantitative MRI data (e.g., from diffusion-weighted [66- 69] and resting-state functional MRI sequences [69, 70]), these algorithms can accurately identify MS patients, achieving classification accuracies ranging from 83.7% to 90.0% [71]. This highlights AI's potential to identify subtle patterns and relationships that support diagnostic and prognostic assessments [66–68].

6. Current Treatment and Future Perspectives

Historically, conventional approaches to MS treatment focused on preventing and managing acute attacks and modifying lifestyle, often employing broad immunosuppression to reduce CNS deterioration and diminish disability, as illustrated in Figure 3. Despite some success, these treatments frequently presented numerous, and at times severe, potential side effects [20]. Furthermore, these traditional therapies largely failed to address the underlying pathology of the disease, particularly the inability to promote remyelination and effectively treat progressive MS. However, significant breakthroughs in stem cell therapy and immune modulation, combined with novel biomedical engineering approaches, have opened new avenues for therapy. These emerging therapeutic strategies are increasingly patient-tailored, aiming to remyelinate specific structures through regenerative approaches, thereby potentially reversing the course of the disease. Several promising therapeutic approaches have been devised over recent years, each demonstrating encouraging outcomes in preclinical and clinical trials [73].

Summary of Disease-Modifying Therapies (DMTs): The growth in the discovery of early disease-modifying treatments (DMTs) has paralleled advances in understanding MS pathology. Earlier preclinical work emphasized the proliferation of autoreactive cells, particularly T cells, in peripheral lymphoid organs, their subsequent migration, and residence in the CNS, leading to focal pathology. However, clinical trials focused

exclusively on T-cell treatments have shown limited success for relapsing MS (RMS) patient groups (Table 2) [73].

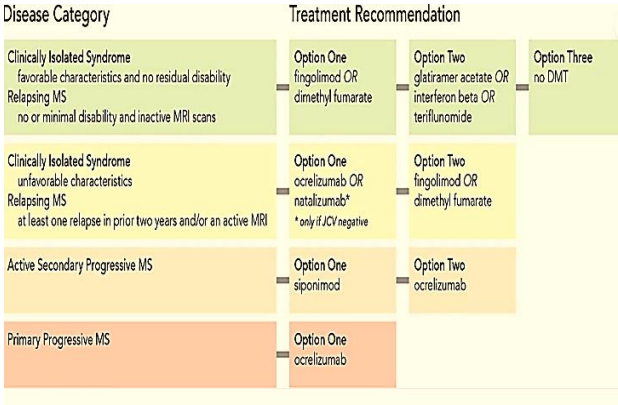

Figure 3. Treatment Recommendations by Disease Category

Table 2. Types of Disease-Modifying Therapies (DMTs)

Aspect	Injectable DMTs	Oral DMTs	Monoclonal Antibody
Development	1st generation therapies; advancing with regenerative approaches like stem cells [74].	Developed for better patient compliance via oral dosing [72, 76].	Advanced immuno-engineered therapies following injectables and orals [75].
Efficacy	Promising results in reversing disease in trials [74].	Reduced relapse rates by 36–58% over 2 years.	Highly effective in lowering relapse rates in RMS [75].
Mechanism	Immune modulation; newer focus on regeneration	Mainly act through S1P receptor modulation	Block immune cell migration into the CNS (e.g., Natalizumab)
Key Feature	Personalized regenerative potential [74].	Improved convenience and adherence [72, 76].	Targeted, high-potency therapies; first-in-class Natalizumab [75].

Non-Conventional Overview of Stem Cells: Table 3 showing the different applications of neural stem cells (NSCs) for MS treatment stems from an enhanced understanding of CNS repair mechanisms. Major CNS repair mechanisms can be broadly categorized into inflammatory and plasticity-dependent pathways [78]. Activation of the pro-inflammatory pathway can lead to a functional reorientation in the CNS, where immune components favor tissue repair through neurotrophic support.

Remarkable advances have occurred in the treatment of MS due to a deeper understanding of its pathogenesis and disease course. Highly effective treatments have achieved near-complete suppression of relapsing disease and focal brain inflammation. However, addressing disease progression remains an unmet need, as current therapies offer incomplete protection against the neurodegenerative component of MS. Although natural history cohorts indicate that the long-term disease course has been significantly improved since the advent of modern treatments, further clinical and real-world studies are essential to provide long-term efficacy and safety data for these therapies. Additional studies on the value of highly effective drugs for early treatment and the identification of patients who derive maximum benefit will also be crucial as we strive towards delivering evidence-based and personalized management and treatment strategies for MS.

7. Conclusion

Multiple sclerosis is a complex and lifelong neurological condition that significantly affects patients' physical, psychological, and social well-being. This review highlights the importance of early diagnosis and continuous treatment as essential strategies for managing symptoms and improving quality of life. Beyond pharmacological interventions, psychosocial support—such as psychological counseling and community engagement—plays a critical role in comprehensive care. A holistic, patient-centered approach that integrates medical and emotional support is essential for addressing the multifaceted challenges faced by individuals with MS. As therapeutic innovations continue to emerge, sustained public awareness, personalized care, and empathy remain fundamental to empowering patients to live with dignity, resilience, and hope.

Conflict of Interest

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

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Table 3. Neural Stem Cells (NSCs) Bioengineering in MS

Aspect	Neural Stem Cells (NSCs)	Induced Pluripotent Stem Cells (iPSCs)	Biomaterials for NSCs & iPSCs	Nano-Biomedical Engineering for Systemic Delivery
Key Role in MS	Show regenerative potential by differentiating into neuronal and glial cells; capable of crossing the blood–brain barrier [77].	Enable patient-specific regeneration; reprogrammed from somatic cells using key transcription factors (e.g., KLF4, NANOG) [78].	Support survival and maturation of transplanted stem cells in hostile CNS environments [79–84].	Enhance targeting, survival, and tracking of IV-delivered stem cells using magnetic nanoparticles [85, 86].
Delivery Method	Direct CNS implantation.	Reprogrammed cells prepared for CNS application.	Typically, via spinal cord injection with supportive matrices.	Intravenous delivery guided by external magnetic fields.
Limitations & Advances	Still in preclinical stages; both direct and indirect regeneration reported [77].	Bypasses ethical issues of embryonic stem cells; ongoing optimization needed [78].	Hydrogels and ECM scaffolds improve integration in inflammatory tissues [79–84].	Nanotech improves engraftment and migratory control; systemic fate remains under study [85, 86].

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