v. 5, n. 23, 2025

International Journal of Health Science

Acceptance date: 28/05/2025

MULTIPLE SCLEROSIS: PATHOPHYSIOLOGY AND TREATMENT

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Abstract: Multiple sclerosis (MS) is a chronic inflammatory and autoimmune disease that affects the central nervous system and is marked by demyelination and axonal degeneration, which compromises nerve conduction and leads to progressive neurological deficits. This literature review discusses the pathophysiology of MS, highlighting the role of T and B lymphocytes in the autoimmune response and the importance of compartmentalized inflammation in the progressive forms of the disease. In addition, typical clinical manifestations are described, such as muscle weakness, fatigue, visual, cognitive and sphincter alterations, which significantly impact patients' quality of life. The study also looks at the evolution of MS treatment, with an emphasis on the early use of high-efficacy disease-modifying therapies (HETA), such as ocrelizumab, which demonstrate better long-term functional outcomes. Other emerging approaches include immunosuppressants, cell therapies (such as TACTH), remyelinating agents, BTK inhibitors and neuroprotectants. In addition to pharmacological treatment, rehabilitation strategies such as telerehabilitation, virtual reality and transcranial stimulation have shown efficacy in improving patients' mobility, cognition and well-being. Although therapeutic advances are notable, challenges remain, especially in the treatment of progressive forms of the disease. The search for biomarkers and personalized interventions, combined with the development of technologies such as artificial intelligence and big data, point to a promising future in the construction of precision medicine aimed at controlling MS and preserving patients' functionality and autonomy.

INTRODUCTION

Multiple sclerosis (MS) is a chronic, inflammatory and demyelinating autoimmune disease of the central nervous system (CNS), characterized by an immune-mediated attack

on myelin and neuronal axons, resulting in progressive neurodegeneration. It represents the main cause of non-traumatic neurological disability in young adults, predominantly affecting individuals between the ages of 18 and 50, with a higher prevalence in females. (DUAN et al., 2023; HAUSER; CREE, 2020) It is estimated that approximately 2.5 million people worldwide live with the disease, whose clinical course is widely variable, encompassing recurrent-remitting, secondary progressive and primary progressive forms, with varying degrees of severity and functional impact. (DUAN et al., 2023; HAKI et al., 2024)

From an immunopathological point of view, MS involves a complex process in which T helper lymphocytes (CD4+), particularly the Th1 subtype, play a central role in activating inflammatory responses against myelin, often triggered after viral infections. In addition to the inflammatory response mediated by Th1 T helper cells, there is growing evidence of the critical involvement of B cells in perpetuating the autoimmune response. These cells act not only as producers of antibodies against myelin components, but also as potent antigen presenters for T cells, amplifying the inflammatory process in the CNS. Recognition of the importance of B-cells in the pathogenesis of MS has prompted the development of B-cell depleting therapies, such as ocrelizumab, which have shown efficacy in reducing new inflammatory lesions and the clinical progression of the disease (DUAN et al., 2023; HAUSER; CREE, 2020). This pro-inflammatory response leads to myelin destruction, axonal loss and the formation of gliosis plaques, classic histopathological features of the disease. Recently, the relevant contribution of B lymphocytes in the pathophysiology of MS has also been recognized, which has important implications for the development of targeted therapeutic strategies (DUAN et al., 2023; HAKI et al., 2024).

In addition to the peripheral immune response, there is evidence that compartmentalized inflammation also occurs in the CNS, especially in the progressive forms of the disease. These forms involve meningeal infiltration and persistent activation of microglia, which contributes to continuous and irreversible neurodegeneration (SELMAJ et al., 2024).

Compartmental inflammation in progressive forms of MS is related to the presence of ectopic lymphoid follicles in the meninges and the persistent activation of microglia. These phenomena contribute to a chronic neurotoxic environment that is less responsive to conventional anti-inflammatory therapies, highlighting the need for therapeutic approaches that act directly on microglia and intracerebral neurodegenerative processes (SELMAJ et al., 2024).

Clinically, the disease is manifested by recurrent neurological outbreaks that affect multiple functions, such as motor skills, coordination, sensitivity, sphincter control, cognition and emotional state. These episodes, when cumulative, generate persistent neurological impairments, significantly damaging patients' functional autonomy and quality of life. (DUAN et al., 2023; HAKI et al., 2024) The most frequent symptoms include muscle weakness, spasticity, tremors, ataxia, intense fatigue, urinary and intestinal dysfunction, visual alterations, neuropathic pain, dysarthria, dysphagia and cognitive and psychiatric disorders. (DUAN et al., 2023)

Health-related quality of life (HRQoL) has emerged as a key construct in assessing the overall impact of MS. A recent systematic review analyzed 27 studies on HRQoL in MS patients, identifying significant impairment in multiple domains, including physical functioning, vitality, mental health and social participation (Da Silva et al., 2024). Factors such as fatigue, pain, cognitive dysfunction and physical disability showed a consistent negative correlation with HRQoL measures. Interes-

tingly, psychosocial variables such as perceived social support, adaptive coping strategies and sense of coherence emerged as important moderators of the relationship between disease severity and quality of life, suggesting potential targets for psychosocial interventions.

In recent years, the therapeutic paradigm for MS has undergone significant changes. Traditionally, a staggered strategy was used, starting treatment with low-efficacy disease-modifying drugs (LETA), reserving more potent agents for refractory cases. However, recent evidence from randomized clinical trials and long--term population studies has shown that early treatment with high-efficacy drugs (HETA) is associated with a lower rate of flare-ups, less progression of disability and better neurological outcomes at up to 10-15 years of follow-up, regardless of the initial inflammatory burden or the patient's prognostic profile (HAUSER; CREE, 2020; SELMAJ et al., 2024).

In addition to immunomodulatory therapies, new therapeutic strategies are being investigated, such as Bruton's tyrosine kinase (BTK) inhibitors, which act to modulate microglia, as well as stem cell approaches for regeneration. Another highlight is neurological rehabilitation, which uses virtual reality, transcranial stimulation and robotics, with the aim of neuroplasticity and functional restoration (DUAN et al., 2023).

Rehabilitation therapies have been gaining prominence as complementary tools in the management of MS. Strategies such as virtual reality, repetitive transcranial magnetic stimulation (rTMS), transcranial direct current stimulation (tDCS), and robot-assisted gait training have shown significant functional improvement, especially in reducing fatigue, improving cognition and balance. Such interventions positively modulate neuroplasticity and reduce peripheral inflammatory cytokines such as IL-4 and IL-10, also contributing to improving the patient's systemic inflammatory state (DUAN et al., 2023).

There are studies that indicate a significant association between infection with *Mycobacterium avium* subspecies *paratuberculosis* (MAP) and increased risk of developing MS, with odds ratios greater than 10 when analyzing anti-MAP antibodies and MAP DNA, highlighting the role that environmental triggers play in the pathogenesis of the disease (EKUNDAYO et al., 2022).

This new therapeutic model seeks to exploit an early window of opportunity in which intervention with potent anti-inflammatory agents can more effectively modify the natural history of the disease, preventing the onset of irreversible deficits. In addition, developments in the safety profile of HETA have contributed to greater clinical acceptance, favoring their use as first-line treatment, especially in cases with a high risk of progression. (SELMAJ et al., 2024) The current approach therefore emphasizes the proactive management of MS, with early initiation of effective interventions, strict control of inflammatory activity and multidisciplinary symptomatic treatment, including physiotherapy, specific pharmacotherapy for spasticity, incontinence and constipation, among other aspects. (HAKI et al., 2024; HAUSER; CREE, 2020)

Given the multifactorial impact of the disease and the complexity of its management, it is essential to have a thorough understanding of the pathophysiology of multiple sclerosis, its clinical forms and recent advances in the therapeutic arsenal, in order to propose increasingly effective and individualized interventions for the patient.

METHODOLOGY

This study is a bibliographic review aimed at gathering the most current and relevant evidence related to diagnostic strategies for multiple sclerosis, considering the advances and perspectives described in recent literature. To carry out the research, a systematic search was carried out in the PubMed databa-

se, considering publications from the last five years. The descriptors used in the search were: "Multiple Sclerosis", "Diagnosis", "Treatment" and "Management", combined to ensure the comprehensiveness and specificity of the results obtained.

We included articles published during the period in question, which directly or indirectly addressed the methods of diagnosing multiple sclerosis, and which were available in full text on the database consulted. Publications written in different languages were accepted, as long as they were accessible and understandable, and presented thematic relevance, methodological consistency and scientific contribution to the subject. Original studies, narrative reviews and update articles were included. Duplicate publications, studies outside the proposed scope and articles not available on the PubMed platform were excluded.

RESULTS AND DISCUSSION

Multiple sclerosis (MS) is an inflammatory, chronic, autoimmune neurological disease characterized by an attack by the immune system against myelin - the substance that coats and insulates nerve fibres in the central nervous system (CNS). The destruction of myelin compromises the conduction of nerve impulses, resulting in varied symptoms such as muscle weakness, visual alterations, motor and cognitive dysfunctions, as well as intense fatigue. The pathophysiological process involves the activation of autoreactive T lymphocytes, which cross the blood-brain barrier and promote local inflammation, recruiting other immune system cells and releasing pro-inflammatory cytokines. This immunological cascade triggers demyelination and axonal damage, which are the main causes of progressive neurological disability. MS presents itself in different clinical forms, the most prevalent being the relapsing-remitting form (RRMS), characterized by neurological outbreaks followed by partial or complete remissions. In more advanced stages, many patients progress to the secondarily progressive form, marked by a more constant and less reversible functional decline (HAKI et al., 2024).

In the therapeutic context, the current approach to MS is centered on modifying the course of the disease using immunomodulatory and immunosuppressive drugs. These treatments aim to reduce the frequency and severity of relapses, slow down the progression of disability and its occurrence, and limit the inflammatory activity observed through magnetic resonance imaging. It is important to note that the positive effect of early intervention has been observed both for relapse--dependent progression and in patients with relapse-independent progression. (SELMAJ et al., 2024) The main drugs used include beta interferons, glatiramer acetate, sphingosine--1-phosphate receptor modulators (such as fingolimod and siponimod), as well as monoclonal antibodies such as natalizumab and ocrelizumab, which act by inhibiting the migration of inflammatory cells to the CNS or by depleting specific populations of B lymphocytes. Treatment selection should take into account the disease activity, risk factors for adverse effects and the patient's lifestyle. Continuous monitoring, with clinical and radiological examinations, is essential to assess the efficacy and safety of the treatment, allowing for timely adjustments according to the therapeutic response. (SELMAJ et al., 2024)

Patients who start HETA in the first few years after diagnosis have a significantly lower risk of progression to high EDSS scores, as shown by studies of the cohort, such as MS-Base and BMSD. This benefit is observed even in patients with a prognosis considered "benign", which means that the concept of benign MS could be revised, given its often transitory nature. (SELMAJ et al., 2024)

In addition to disease-modifying therapies, there is growing interest in therapeutic strategies aimed at promoting neuroprotection and regeneration. These approaches seek to preserve axons, stimulate remyelination and restore lost neurological functions. Pre-clinical studies with mesenchymal stem cells, oligodendrocytes derived from pluripotent cells and neurotrophic factors have shown potential in inducing neural regeneration and modulating the inflammatory response. Early-stage clinical trials are being conducted to assess the efficacy and safety of these therapies in humans. In addition, research into Bruton's tyrosine kinase (BTK) inhibitors has revealed promising effects in reducing inflammatory activity and modulating microglia, pointing to a new therapeutic horizon in the treatment of progressive MS. These innovations represent a paradigm shift in the management of the disease, which no longer focuses exclusively on containing inflammation but also includes reparative interventions, with the aim of preserving neurological function and improving quality of life in the long term (DUAN et al., 2023).

Cell therapies, particularly autologous hematopoietic stem cell transplantation (AHSCT), have shown impressive results in patients with highly active forms of MS. A recent systematic review evaluated the benefits of cell therapy in MS patients, showing a significant improvement in quality of life, a reduction in inflammatory activity and stabilization of disease progression in up to 70% of treated cases (BORGES et al., 2024). TACTH acts by "rebooting" the immune system, eliminating self-reactive cells and allowing the reconstitution of a more tolerant immune repertoire. Despite the promising results, this approach still presents considerable risks, including procedure-related mortality of 0.5-2%, which restricts its indication to selected cases of aggressive disease refractory to conventional therapies.

Remyelination and neuroprotection strategies are another area of intense research. Researchers at the Butantan Institute recently identified a promising therapeutic target from rattlesnake venom. In experimental models, the use of this toxin prevented the development of the disease in 40% of the animals, significantly reduced neuropathic pain and prevented atrophy and loss of muscle function (TEXEIRA et al., 2019). Other agents under investigation include antibodies against LINGO-1 (opicinumab), clemastine, bexarotene and methylthiouracil, all of which have the potential to stimulate oligodendrocyte differentiation and promote remyelination.

A systematic review and meta-analysis published in 2024 by Cochrane (RIDLEY et al., 2024) evaluated the efficacy and safety of immunomodulators and immunosuppressants in progressive MS. 23 studies were analyzed involving more than 10,000 participants. This analysis identified that only Rituximab and Interferon beta-1b showed moderate evidence of a small reduction in the number of flares at 24 and 36 months, respectively. However, data on disability progression remained of low or very low certainty.

Also according to Cochrane, serious adverse events were rarely identified with confidence, and discontinuation rates due to adverse effects were slightly higher for several drugs, such as interferons, rituximab, natalizumab, ocrelizumab and fingolimod. In conclusion, there is a lack of head-to-head studies with follow-up of more than three years, and the impact on quality of life and cognition should be better assessed in future studies

Doherty et al.(2024) in a systematic review and meta-analysis showed the effectiveness of telerehabilitation in improving mobility and balance in people with MS. This analysis included five randomized clinical trials with 225 participants, showing statistically and clinically significant effects on both mobility

(SMD = 0.41; 95% CI: 0.05-0.77; p = 0.02) and balance (SMD = 0.64; 95% CI: 0.31-0.97; p = 0.0001). Virtual games (exergames), virtual reality platforms and pilates guided by videoconference were used as resources.

Telerehabilitation is a useful tool, especially because it can bypass logistical barriers faced by people with MS, such as difficulty getting around and high travel costs, representing a viable alternative to face-to-face clinics. These data further emphasize the role of neuroplasticity and the importance of personalizing biofeedback-based interventions as effective strategies for functional rehabilitation, even in home environments.

Currently, the approach to multiple sclerosis is multifaceted, combining early and effective pharmacological treatments, along with personalized symptomatic and rehabilitation strategies, aimed at containing inflammation while preserving patients' function and quality of life.

There is a growing movement towards identifying serum and cerebrospinal fluid biomarkers, such as neurofilament light chain (NfL), which can predict subclinical inflammatory activity and the risk of early progression. Although promising, these markers still face challenges in terms of specificity and individual applicability. In the field of neuroprotection, current research focuses on the use of neurotrophic factors, such as BDNF, and LINGO-1 inhibitors, which stimulate remyelination and may favorably modify disease progression (SELMAJ et al., 2024; HAUSER; CREE, 2020).

CONCLUSION

Multiple sclerosis (MS) remains one of the greatest challenges facing contemporary neurology, marked by its unpredictable nature, heterogeneous course and complex pathophysiology, involving immune-mediated mechanisms and simultaneous neurodegenerative processes. Current understanding recognizes the central role of T and B lymphocytes, as well as neuroglial inflammation, in perpetuating axonal damage and demyelination.

Modern therapeutic management of MS requires a paradigm shift: from a staggered approach to early intervention strategies with highly effective therapies capable of significantly altering the course of the disease. Personalization of treatment, guided by biomarkers and continuous clinical monitoring, has proved essential to preserve neurological function and promote long-term quality of life.

However, there are still important therapeutic gaps, especially in the treatment of progressive MS, where the response to drugs remains limited and based on less robust evidence. In this scenario, functional rehabilitation - especially telerehabilitation - has emerged as a promising, safe and highly adherent alternative, contributing to the recovery of motor and cognitive functions, as well as expanding access to specialized care.

The future of MS care lies in the convergence of multiple fronts: innovative immunomodulatory therapies, neuroprotection strategies, psychosocial support and integrated and personalized rehabilitation programs. The growing use of clinical, neurophysiological and neuroimaging biomarkers, combined with emerging technologies such as artificial intelligence, wearable sensors and big data analysis, will enable the construction of predictive algorithms and therapeutic plans adjusted in real time, bringing clinical practice closer to the concept of precision medicine.

To consolidate this progress, it is essential to invest in longitudinal studies, the validation of biomarkers and the development of accessible technological solutions, ensuring that MS ceases to be a disabling condition and becomes a manageable disease, with a focus on preserving patients' autonomy and functionality.

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