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Multiple Sclerosis: Current Perspectives on Disease Mechanisms, Clinical Management, and Therapeutic Advances

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Abstract

Background: Multiple sclerosis (MS) is a disease whose incidence has been increasing statistically alongside the development and wider availability of advanced diagnostic methods. Despite extensive research investigating its etiology, clinical course, and therapeutic approaches, considerable uncertainty remains regarding many aspects of the disease.

Aim: This review aims to synthesize current scientific evidence, contextualize recent findings within the existing database of literature, and relate them to the practical needs of patients living with MS.

Materials and Methods: A literature search was conducted using the PubMed, Google Scholar, MEDLINE, and Journal of Education, Health and Sport (JEHS) databases. Relevant studies and meta-analyses addressing various aspects of this complex and heterogeneous disease were identified and analyzed.

Results: The available evidence clearly indicates that, owing to its high diagnostic sensitivity, magnetic resonance imaging (MRI) remains the gold standard for the diagnosis of MS. Therapeutic management continues to rely predominantly on well-established immunosuppressive and immunomodulatory agents, which constitute the cornerstone of current treatment strategies.

Conclusions: Current knowledge has enabled the identification of emerging directions in MS diagnostics, including the increasing use of Visual Evoked Potentials (VEP), Optical Coherence Tomography (OCT), and greater recognition of the nonspecific clinical manifestations that may accompany the disease. This review also highlights existing research gaps concerning more selective therapeutic approaches, such as alemtuzumab, cladribine, and chimeric antigen receptor T-cell (CAR-T) therapy. Furthermore, theoretical and patient-centered domains—including mental health and sexual functioning among individuals with MS—remain insufficiently explored and warrant further investigation in future research.

Keywords: *Multiple sclerosis, autoimmune disorder, demyelination, nonspecific clinical presentation, MRI, immunoregulators, CAR-T, mental health, sexuality*

1. Introduction

Multiple sclerosis (MS) is a immune-mediated demyelinating neurodegenerative disease causing such physical symptoms as muscle weakness, muscle spasms, decreased mobility and balance, and increased sensitivity to pain, with psychiatric episodes and fatigue leading to severe disability and deterioration of quality of life.¹ The disease appears also through visual disturbance, sensory disorders, chronic pain, cognitive impairment, mental disorders, urinary, defecation and

sexual disorders. Central nervous system is the target of the inflammatory response. It seems to begin when autoreactive T cells cross the blood-brain barrier (BBB) and provoke specific cascades in the CNS, leading to inflammation and axonal degeneration, although it is not clear what causes T cells activation.² However, the success of B-cell targeted therapies challenges the standard T-cell autoimmune dogma.³ The International Advisory Committee on Clinical Trials of MS defined four MS phenotypes: clinically isolated syndrome (CIS), relapsing remitting MS (RRMS), primary progressive MS (PPMS), and secondary progressive MS (SPMS).⁴ The therapy includes symptomatic treatment such as myorelaxants (baclofen, tizanidine, benzodiazepines), coanalgesics treating neuropathic pain (carbamazepine, pregabalin, gabapentin, imipramine), facilitating urination – drugs (cholinolytics, cholinomimetics, α -adrenomimetics, α -adrenolytics), phosphodiesterase inhibitors treating sexual disorders (sildenafil, tadalafil)⁵ and causal treatment (interferon - β , glatiramer acetate, dimethyl fumarate, diroximel fumarate, teriflunomide, ozanimod, ponesimod, ofatumumab, ocrelizumab, ublituximab, ocrelizumab, fingolimod, natalizumab, alemtuzumab and cladribine). In recent years, new therapeutic strategies have emerged – CAR-T method is one of them.

2. Materials and Methods

A literature search was conducted using the PubMed, Google Scholar, MEDLINE, and Journal of Education, Health and Sport (JEHS) databases. Relevant studies and meta-analyses addressing various aspects of this complex and heterogeneous disease were identified and analyzed. The search included studies published between 1998 and 2026. The following keywords and their combinations were used: "multiple sclerosis", "autoimmune diseases", "demyelinating diseases", "MRI, immunoregulators", "CAR-T", "MS symptoms", "MS diagnosis", "MS treatment" and "MS prognosis." Inclusion criteria included: studies conducted in humans, focusing on the symptoms, diagnosis, treatment, and prognosis of multiple sclerosis. Exclusion criteria included: studies older than 1997.

3. Results

3.1. Epidemiology and pathomechanism

The disease decreases quality of life in young adults between 20 and 40 years old, but it can also occur at younger and older ages and it affects women 3 – times more than men.² Multiple sclerosis (MS) is reported to affect 2.8 million people worldwide in recent years⁶ and almost 60 thousands in Poland in 2023.⁷ MS occurs most often in countries with a temperate climate (Northern Europe, northern areas of the USA, Canada). This relationship may be caused by vitamin D deficiency, which is suspected to be one of the etiological factors. MS aetiology remains unclear; interactions between environmental and genetic factors appear to promote the disease. The main

genetic risk factor for multiple sclerosis is the HLA-DRB1*15 genotype and/or other strongly linked gene variants. Carriers of the HLA-DRB1*15:01 allele in a heterozygous pattern have more than three times higher risk of developing multiple sclerosis, and those with the homozygous genotype have more than six times higher risk of developing multiple sclerosis.⁸ In addition to genetics, environmental factors such as obesity, tobacco use, microbiota alterations, Epstein–Barr virus (EBV) infection or vitamin B deficiency is also considered playing an important role in progression of the disease.² Symptomatic EBV infection (infectious mononucleosis) doubles the risk of MS.⁹ The causal relationship between EBV infection and the development of MS is explained by the molecular similarity theory¹⁰ and the immortalization of B lymphocytes by the virus.¹¹ Research is currently focusing on the influence of the gut microbiota (GM) on the onset and development of MS. GM is the combination of bacteria, fungi, archaea, eukaryotes, and viruses that reside in the intestinal mucosa. Actinobacterium, Bacteroidetes, Firmicutes, Fusobacteria, Proteobacteria, and Verrucomicrobia are the main phyla that compose it. GM microorganisms may impact on the CNS through complex interaction well-known as the gut–brain axis (GBA). It is a set of neurochemical signals that influence the proper function and homeostasis of the digestive system, which plays an important role in gastrointestinal function modulation such as motility, secretion, blood flux regulation, intestinal permeability, immunity activity, and visceral sensations, including pain. Gut microbiota affects the brain through signals transmitted via chemical substances received by afferent fibers of the vagus nerve. The main pathophysiological factor responsible for inducing MS is inflammatory changes due to excessive immune response, similarly as in autoimmune diseases such as type 1 diabetes and Hashimoto's thyroiditis. Therefore, factors that limit the inflammatory response should reduce the risk of developing this disease. This effect is exerted by SCFAs [butyric acid (BA), acetic acid (AA), and propionic acid (PA)], which inhibit T helpers cells and stimulate regulatory T cells. SCFAs are produced in the colon from non-digestible carbohydrates by bacteria and regulates inflammatory processes by reducing Th 17 lymphocytes and the maintaining balance of the levels pro- and anti-inflammatory cytokines. Clinical studies indicate decrease in Firmicutes, Lachnospiraceae, Bifidobacterium, Roseburia, Coprococcus, Butyricicoccus, Lachnospira, Dorea, Faecalibacterium, and Prevotella phylum and an increase in phylum Bacteroidete. Most of these bacteria play a key role in the production of SCFAs.²

Traditionally, two phases of MS are distinguished: the first involves inflammation which is responsible for the relapsing-remitting form, and the later phase of neurodegeneration is responsible for the primary and secondary progressive forms. However, the effectiveness of treatment in different phases of the disease casts doubt on the current views on the two-stage natural course of multiple sclerosis.¹² Charcot noted "sclerotic plaques" in the periventricular region, pons, and spinal cord.¹³ Inflammatory changes around the veins progress, leading to the formation of demyelinating plaques.¹⁴

The infiltrates involve T lymphocytes, including CD8⁺ cells, recognized exclusively by MHC class I and less B lymphocytes and plasma cells.¹⁵ In the initial stage, oligodendroglial damage occurs and then axons are affected.¹⁶ Classically in the relapsing-remitting form the lesions are active and the infiltrates consist mainly of lymphocytes, whereas in the progressive form, the lesions are surrounded by microglial cells and macrophages.¹⁷ Furthermore, increased secretion of pro-inflammatory cytokines such as lymphotoxin, tumour necrosis factor (TNF-), and interleukin (IL)-6, or deficient production of regulatory cytokines including IL-10 or IL-35 may impact activation of complement system and T lymphocytes. High ROS, RNS and NO levels results oxidative injury through mitochondrial chain complexes. Both energy imbalance and Ca²⁺ excitotoxicity lead to demyelination.¹⁸ These changes cause progressive brain atrophy at a rate of 0.5% per year, which is 2-3 times faster than in healthy individuals.¹⁸

3.2. Clinical types of disease

The course of multiple sclerosis is highly variable; nevertheless in most patients, multiple sclerosis is characterized by the onset of recurring clinical symptoms followed by total or partial recovery, namely, the classic relapsing-remitting form of multiple sclerosis (RRMS).¹⁸ Multiple sclerosis relapses usually develop subacutely over hours or days, reaching a steady state (plateau) lasting for several weeks, followed by gradual improvement.¹⁹ After 10–15 years of disease, this pattern becomes progressive in up to 50% of untreated patients, during which time clinical symptoms slowly cause progressive deterioration over a period of many years. This disease stage is defined as secondary progressive multiple sclerosis (SPMS).¹⁸ The most common initial symptom of primary progressive multiple sclerosis is progressive spastic paraparesis of the lower limbs, then sensory ataxia, cerebellar ataxia, cognitive impairment, and progressive visual deterioration.¹⁹ In about 15% of patients with multiple sclerosis disease progression is relentless from onset [primary progressive multiple sclerosis (PPMS). Actual diagnosis of PPMS requires presence of clinical progression lasting at least 1 year, as well as two of the following three criteria: brain or spinal cord lesions on MRI indicating dissemination of disease, or positive CSF findings.¹⁸

3.3. Symptoms

Given the critical importance of early diagnosis of multiple sclerosis (MS), particular attention should be paid to the potential clinical manifestations of this neurological disorder. Considering that the pathophysiological mechanism of MS is based on an exaggerated and inappropriate autoimmune response directed against the myelin sheath and, to some extent, the axons of neurons within the central nervous system (CNS), understanding the clinical expression of impaired neural conduction becomes considerably more intuitive.²⁰

According to the most recent literature, the symptoms that characterize the initial stages of

MS predominantly involve sensory dysfunction. Numbness of the limbs or face, generalized paresthesia, the sensation of an electric shock radiating along the spine (Lhermitte's sign), and disturbances in temperature and pain perception are recognized manifestations of the early phase of this debilitating disease. Such clinical presentations may reflect ongoing damage to the sensory pathways of the spinal cord or the thalamus.

Progressive demyelination of upper motor neurons, which disrupts the proper transmission of neural signals to lower motor neurons, contributes to the development of limb weakness, increased fatigability, reduced muscle strength, spasticity, and frequent muscle spasms.

Clinical observations also indicate the significant impact of impaired coordination and integration of information originating from the vestibular, visual, and proprioceptive systems on the maintenance of balance. Because of disrupted communication between these systems, patients commonly exhibit gait instability, clumsiness, cerebellar ataxia, and dizziness.

The widespread inflammatory process affecting the CNS contributes substantially to the chronic fatigue experienced by many individuals with MS. Fatigue, which can be defined as a "significant lack of physical and/or mental energy that is perceived by the individual or caretaker to interfere with usual or desired activity," is one of the most common and debilitating symptoms of MS. This condition negatively impacts quality of life, as measured by HRQL instruments. Furthermore, chronic fatigue leads to increased unemployment and physical, psychological, and financial burden on caregivers, which translates into higher healthcare costs.²¹ The continuous burden placed on the nervous system and its compensatory mechanisms results in increased energy expenditure required for effective conduction of nerve impulses through already damaged neural fibers. Consequently, disrupted neuronal function and impaired axonal signaling interfere with the synthesis and release of neurotransmitters, which play a crucial role in maintaining physiological homeostasis.²²

The clinical presentation described in both the scientific literature and clinical practice is further expanded by symptoms involving cognitive functioning, which are strongly associated with documented damage to the white matter and cerebral cortex.²³ Both the disruption of communication between different brain regions and the loss of axonal integrity contribute to deficits in memory processes, including impaired consolidation and retrieval, cognitive slowing often described as "brain fog," and attentional difficulties characterized by distractibility and reduced concentration.

Regardless of the severity of their manifestation, all the symptoms and mechanisms may also affect another highly significant yet frequently underexplored aspect of functioning: mental health and sexuality. Awareness of the limitations imposed by a diagnosis of multiple sclerosis, together

with persistent anxiety regarding the possibility of future disease relapses, may contribute to the development of depressive disorders, anxiety disorders, and substance-related addictions. Furthermore, because living with MS alters body image and an individual's relationship with their own body, while simultaneously exerting a profound impact on interpersonal relationships and the broader social system in which the patient functions, many individuals report decreased libido, erectile dysfunction, and orgasmic disorders. These difficulties may also have a direct neurological basis.²⁴

Despite the increasing accuracy and widespread availability of diagnostic methods used to detect or confirm multiple sclerosis, including magnetic resonance imaging (MRI) for lesion visualization, lumbar puncture (LP), Visual Evoked Potentials (VEP), and Optical Coherence Tomography (OCT), awareness of the frequent occurrence of characteristic symptoms or their atypical constellations, often contributes to improved prognostic outcomes among patients diagnosed with this condition.²⁵

3.4. Diagnosis

Imaging methods (mainly MRI) play a major role in diagnosing MS. MRI is about 5 to 10 times more sensitive to ongoing inflammatory demyelination than clinical assessment. The clinical value of MRI is increased by the administration of contrast agents that enable the detection of blood-brain barrier disruption.¹⁸ A characteristic feature is disseminated both in time and space lesions throughout the central nervous system (i.e., damage to different areas of the central nervous system at different times). The simultaneous presence of both enhancing and non-enhancing MS-typical MRI lesions is helpful in determining dissemination in time (DIT). For dissemination in space (DIS) periventricular, cortical or juxtacortical, infratentorial, and spinal cord lesions are crucial to find them. MS lesion measures at least 3 mm longitudinally and is hyperintense in T2/FLAIR. On T1 weighted images the plaques are iso or hypointense, black holes, due to inflammatory edema in fresh and axonal loss in chronic plaques.

There are characteristic radiological signs. Periventricular lesions tend to be triangular with their bases along the ventricle and perpendicular to the calloso-septal margin – Dawson's Fingers. Hypointense lesions located around the central vein on T2 and FLAIR sequences (central vein sign), and especially the presence of 6 such lesions in the white matter is helpful to differentiate MS from mimics. Ependymal 'Dot Dash' sign – ependymal hyperintense irregularity on FLAIR images seen along the undersurface of corpus callosum is sensitive for early detection of MS lesion. 3D FLAIR and newer MR sequences like MP-RAGE (Magnetization prepared rapid acquisition with gradient echo), DIR (Double inversion recovery), and PSIR (Phase-sensitive inversion recovery) are promising in helping identify hidden cortical lesions.²⁶

Clinical manifestations depend on the location of the lesions. Some lesions are clinically silent and do not cause symptoms noticeable to the patient or detectable during a neurological examination. However, the pathological process can begin long before the onset of the first clinical symptoms, as evidenced by radiological changes typical of MS, incidentally detected in some individuals during magnetic resonance imaging (MRI) of the head performed for other indications. In such cases, the radiologically isolated syndrome (RIS) is diagnosed. Approximately one-third of individuals with RIS develop clinical symptoms that meet the criteria for MS within 5 years.²⁷

Visual Evoked Potentials (VEP), Auditory Evoked Potentials (AEP) and Somatosensory Evoked Potentials (SEP) are helpful in confirming the diagnosis, in the case of uncertain clinical and radiological symptoms.¹⁹

Another important method to diagnose MS is lumbar puncture, which is crucial to confirm oligoclonal bands in cerebrospinal fluid (CSF). Anti-nuclear factor, vitamin B12, thyroid function, syphilis, HIV-1, HTLV-1 serology are also recommended. Depending on the clinical presentation anti-aquaporin-4 and anti-MOG antibody screening may be indicated.¹⁹ These antibodies prevent in NMOSD i MOGAD, which symptoms are similar to those occurring MS, but affect mainly spinal cord and optic nerve.

The McDonald diagnostic criteria are used to diagnose MS. The latest ones were published in 2024 and introduced several changes compared to the previous ones from 2017. The most important include: the addition of the optic nerve as a fifth location of disease on MRI to demonstrate dissemination in space (DIS), the elimination of the need to demonstrate dissemination in time (DIT) in some situations, and the addition of new diagnostic markers (kappa free light chains (κFLC) in CSF as an alternative to oligoclonal bands, the central vein sign (CVS), and paramagnetic rim lines (PRL) – MRI biomarkers). The new criteria also include other changes that allow for an accelerated diagnosis of MS. The importance of disease relapses has been raised (the symptoms of a disease relapse described by the patient are treated equally to CIS - clinically isolated syndrome) and it has been made possible to make a diagnosis in a patient with RIS - radiologically isolated syndrome if certain conditions are confirmed (DIS + specific biomarkers).²⁸ Detailed recommendations for diagnosing MS in children, seniors, and patients with comorbid vascular conditions have been included. Reports to date indicate that the 2024 criteria enable faster diagnosis in many cases. The improved diagnostic process has specifically included the addition of the optic nerve as a fifth location for MS lesions and the exclusion of the DIT requirement.²⁹ It has been noted that lesions appear much earlier than the first noticeable symptoms. The new criteria also emphasize the need for extreme caution when making a diagnosis. Both a missed or delayed diagnosis and an incorrect diagnosis have negative consequences for patients. It is particularly important to consider and conduct a thorough

differential diagnosis in patients suspected of suffering from MS. However, patients diagnosed with MS should be monitored and their diagnosis continually reviewed.²⁸

3.5. Treatment

The treatment of MS can be divided up into symptomatic therapies that are often used in different disease areas to treat symptoms resulting from neurological dysfunction and disease modifying therapies (DMT) that tend to be MS specific. Historically, treatments have been immunosuppressant (including fingolimod, natalizumab, ocrelizumab), immunomodulators (such as interferon-beta, glatiramer acetate, teriflunomide), or immune reconstitution therapies (including alemtuzumab and cladribine).¹⁹ Side effects include both not very dangerous [flu-like symptoms, local reactions, gastrointestinal disorders (nausea, dyspepsia), hair loss] and serious [basal cell carcinoma, opportunistic infections (progressive multifocal leukoencephalopathy, cryptococcosis etc.), hypogammaglobulinemia, secondary autoimmune diseases, cardiomyopathy, infections (especially varicella zoster virus), lympho- and leukopenia, elevated liver enzymes, gastrointestinal disorders (vomiting, diarrhea), bradycardia, hypertension, bronchospasm].

Natalizumab is a selective adhesion molecule inhibitor that binds to the $\alpha 4$ subunit of human integrin, which is highly expressed on the surface of all leukocytes except neutrophils. Natalizumab specifically binds to $\alpha 4\beta 1$ integrin, blocking its interaction with its receptor - vascular cell adhesion molecule 1 (VCAM-1) and its ligands - osteopontin and the alternatively formed fibronectin domain [junctional segment 1 (CS-1)]. Natalizumab blocks the interaction of $\alpha 4\beta 7$ integrin with addressin mucosal adhesion molecule 1 (MadCAM-1). Generally VCAM-1 is not present in the interstitial space of the brain. Proinflammatory cytokines leads to overexpression of VCAM-1 on endothelial cells and likely on glial cells located near the site of inflammation, so disruption of these molecular interactions prevents the penetration of lymphocytes through the endothelium into the brain. Common adverse reactions during natalizumab treatment include urinary tract infection, nasopharyngitis, urticaria, headache, dizziness, vomiting, nausea, arthralgia, chills, fever, and fatigue. Particular attention should be paid to the increased risk of infection and the rare but serious complication - progressive multifocal leukoencephalopathy. The AFFIRM study, in which natalizumab was administered at a dose of 400 mg IV every four weeks, confirmed the drug's clinical efficacy in reducing the frequency of relapses. The relapse-free rate at one year increased in the study group (76%) compared to the control group (53%). The number of patients with disease progression decreased in the study group (11%) compared to the control group (23%). In addition to improved clinical parameters, there was also improvement in imaging parameters. In the control group, T2 lesions increased by an average of 8.8%, while in the study group, T2 lesions decreased by an average of 9.4%.³⁰

Fingolimod is a sphingosine-1-phosphate receptor modulator. It is the functional antagonist of S1P receptors on lymphocytes and blocks the ability of lymphocytes to escape from the lymph nodes. Animal studies have shown that lymphocyte redistribution reduces the penetration of pathogenic lymphocytes (pro-inflammatory Th17 cells) into the CNS, where they could participate in inflammatory processes and damage to nervous tissue. Adverse reactions to fingolimod include influenza, sinusitis, herpes virus infections, bronchitis, pityriasis versicolor, basal cell carcinoma, lymphopenia, leukopenia, depression, headache, dizziness, blurred vision, bradycardia, atrioventricular block, hypertension, diarrhea, acute liver failure, eczema, alopecia, pruritus, back pain, myalgia, arthralgia, weakness, weight loss, increased liver enzymes [alanine aminotransferase (ALT), gammaglutamyltransferase (GGT), aspartate aminotransferase (AST)]. In the Freedoms study, in which 0.5 mg of fingolimod was administered, a reduction in the relapse-free rate at 24 months was observed in the study group (70%) compared to the control group (46%). Additionally, there was a reduction in the number of new or enlarging MRI lesions in the study group compared to the control group.³¹

Ocrelizumab is a recombinant humanized monoclonal antibody that selectively targets CD20-expressing B lymphocytes. The precise mechanism responsible for the therapeutic effect of ocrelizumab in multiple sclerosis is not fully understood, but it is hypothesized to involve immunomodulation through a reduction in the number and function of CD20-expressing B lymphocytes. The main adverse effects of ocrelizumab are related to immune suppression: upper respiratory tract infection, nasopharyngitis, influenza, sinusitis, bronchitis, gastroenteritis, herpes zoster, conjunctivitis, cellulitis, neutropenia, cough, rhinitis, and decreased serum immunoglobulin G and M levels. Ocrelizumab 600 mg in study WA25046 reduced the number of patients with 12-week confirmed disability progression (30.2%) compared with the control group (34%).³²

Interferons are a group of endogenous glycoproteins with immunomodulatory, antiviral, and antiproliferative properties. Adverse reactions to IFN-beta include: neutropenia, lymphopenia, leukopenia, thrombocytopenia, anemia, asymptomatic AST and ALT elevations, depression, insomnia, headache, diarrhea, vomiting, nausea, pruritus, erythematous rash, maculopapular rash, alopecia, myalgia, arthralgia, injection-site inflammation, and flu-like symptoms. The efficacy of AVONEX in MS was demonstrated in a placebo-controlled trial involving 301 patients (AVONEX n=158, placebo n=143) with relapsing MS characterized by at least two exacerbations in the previous 3 years or one exacerbation per year of treatment if duration was less than 3 years. In this trial, the cumulative rate of progressive disability at the end of the second year was 35% in the placebo group and 22% in the AVONEX group. Progressive disability was measured as a 1.0-point increase in the EDSS that lasted at least six months.³³

Studies in animals and patients with multiple sclerosis indicate that glatiramer acetate stimulates secretion of anti-inflammatory and regulatory cytokines in monocytes, dendritic cells, and B cells which results in modulation the adaptive functions of B and T cells. The most common adverse reactions include infection, influenza, anxiety, depression, headache, vasodilation, dyspnea, nausea, rash, joint pain, back pain, asthenia, chest pain, injection site reactions. In a clinical trial with the participation of patients with relapsing-remitting multiple sclerosis (RRMS), which were diagnosed according to standard criteria and who had experienced at least two neurological attacks (exacerbations) in the preceding two years, the relapse rate was reduced by 32%: from 1.98 in the placebo group to 1.34 in the glatiramer acetate group. The study included 251 patients treated for up to 35 months (Copaxone: n=125; placebo: n=126). The cumulative number of patients who experienced 3-month confirmed disability progression was 29.4% for placebo and 23.2% for Copaxone. Furthermore, Copaxone has been shown to be beneficial compared to placebo in magnetic resonance imaging (MRI) studies in patients with relapsing-remitting multiple sclerosis (RRMS).³⁴

Teriflunomide is an immunomodulatory agent with anti-inflammatory properties that selectively and reversibly inhibits the activity of the mitochondrial enzyme dihydroorotate dehydrogenase (DHO-DH), which functionally interfaces with the electron transport chain. As a result of this inhibition, teriflunomide generally reduces the proliferation of rapidly dividing cells that depend on de novo pyrimidine synthesis. The precise mechanism of teriflunomide's therapeutic effect in MS is not fully understood, but it may involve a reduction in lymphocyte counts. The most frequently adverse reactions in patients receiving teriflunomide (7 mg and 14 mg) includes headache (17.8%, 15.7%), diarrhea (13.1%, 13.6%), increased ALT (13%, 15%), nausea (8%, 10.7%) and alopecia (9.8%, 13.5%). It may also cause heavy menstrual bleeding, paraesthesia, sciatica, and carpal tunnel syndrome. In the TEMSO study 1088 patients with MS were divided into the groups which received 7 mg (n=366) or 14 mg (n=359) of teriflunomide or placebo (n=363) for 108 weeks. All patients had a definite diagnosis of MS [using the McDonald criteria (2001)] and demonstrated a relapsing clinical course with or without progression and had at least one relapse in the year preceding the study, or at least two relapses in the two years preceding the study. Before the study, patients had an Expanded Disability Status Scale (EDSS) score of ≤ 5.5 . The annualized relapse rate decreased by 31%, from 0.54 in the placebo group to 0.37 in the study group (14 mg).³⁵

Alemtuzumab is a humanized monoclonal antibody that binds to the CD52 antigen, present in high concentrations on the surface of T (CD3+) and B (CD19+) lymphocytes, NK cells, monocytes, and macrophages and causes lysis of these cells. The depletion of T and B lymphocytes in the circulation induced by LEMTRADA and the subsequent repopulation may reduce the risk of disease relapse, ultimately delaying disease progression. The most common adverse reactions are upper

respiratory tract infection, urinary tract infection, lymphopenia, leukopenia, headache, localized redness, nausea, urticaria, rash, pruritus, fever and fatigue. The most clinically significant adverse reactions are autoimmune disorders (immune thrombocytopenic purpura, Hashimoto's thyroiditis, nephropathies, cytopenias) and infections. CAMMS323 (CARE-MS I) included previously untreated patients with active multiple sclerosis (MS), defined as at least two relapses in the previous two years. Patients demonstrated a reduction in the annualized relapse rate from 0.39 (study group) to 0.18 (control group), which is a 54% reduction. The control group included patients which were administered IFNB-1a (s.c.). In the control group, 27% of patients demonstrated gadolinium-enhancing lesions on MRI, compared with 15.4% in the study group.³⁶

Cladribine is a nucleoside analogue of deoxyadenosine that induces lymphocyte apoptosis by initiating DNA strand breaks and impairing mitochondrial function. Adverse reactions include herpes labialis, herpes zoster, lymphopenia, neutropenia, rash, alopecia, and an increased risk of malignancies. The efficacy and safety of oral cladribine were assessed in a randomized, double-blind, placebo-controlled clinical trial (CLARITY) involving 1326 patients with relapsing-remitting multiple sclerosis. Patients received placebo (n = 437) or cladribine [3.5 mg/kg (n = 433) or 5.25 mg/kg (n = 456)] for a 96-week (2-year) study duration over two treatment cycles. Patients participated in the study if they had experienced at least one relapse in the previous 12 months. There was a reduction in the annual relapse rate from 0.33 in the control group to 0.14 (57,6% decrease; study group - 3.5 mg/kg cladribine) and 0.15 (54,5% decrease; study group - 5.25 mg/kg cladribine). Patients receiving cladribine showed a relative reduction of 86% in the mean number of T1 Gd+ lesions, 73% in the mean number of active T2 lesions, and 73% in the mean number of active T2 lesions compared to placebo.³⁷

CAR-T involves taking the patient's own immune cells, genetically modifying and multiplying them in the laboratory, and then injecting them back into the body. CD19 chimeric antigen receptor (CAR)-T cell therapies have revolutionized the field of hematological malignancies (such as B cell lymphoma) and have begun to demonstrate curative potential use in autoimmune disease (myasthenia gravis).³⁸ CD20-targeting monoclonal antibodies (mAbs) such as rituximab, ocrelizumab, ofatumumab, and ublituximab have enabled a more precise treatment. They effectively deplete circulating B cells but central nervous system (CNS)-resident B cells (particularly those in meningeal follicles) still persist, because limited permeability of the blood–brain barrier restricts monoclonal antibody distribution to the CNS. It sustains chronic inflammation and contributes to progressive neurodegeneration. Autologous haematopoietic stem cell transplantation (aHSCT) offers a more profound immunoablative effect, but may cause infertility, malignancy, and treatment-related mortality. These limitations are most evident in progressive MS, where existing therapies often fail

to stop disability progression, underscoring the need for novel, tissue-penetrant immunotherapies such as chimeric antigen receptor (CAR) T-cell therapy.³⁹ CAR-T therapy targets CD-19 and BCMA receptors. The pathogenic role of autoreactive B cells in MS is well established. They drive disease by presenting self-antigens, activating autoreactive T cells, and sustaining inflammation in peripheral lymphoid organs and the CNS. Tissue-resident B cells exacerbate local neurotoxicity through proinflammatory cytokine release—including GM-CSF, IL-6, and lymphotoxin- α —especially in progressive MS.³⁹ Individual studies evaluating CAR-T's effectiveness are currently in Phase I or II. Further multicenter clinical trials with larger sample sizes are warranted to assess its clinical efficacy, safety, long-term effects, dosing, technical demands, and costs. CAR-T therapy is associated with an increased risk of ICANS (immune effector cell-associated neurotoxicity syndrome). This is due to uncontrolled proliferation of CAR-T cells after infusion and cytokine release syndrome (CRS). Early symptoms include dysgraphia, speech impairment, tremor, cognitive impairment, and fatigue, which require consistent monitoring. In more severe cases, epileptic seizures, increased intracranial pressure, and even coma can occur.⁴⁰

The scale used to assess the effectiveness of treatment is NEDA. It is defined based on clinical indicators (NEDA 1 and NEDA 2 – no relapses or clinical progression), inflammatory activity on MRI (NEDA 3), and brain atrophy on MRI and biological indicators (NEDA 4 and NEDA 5 – NFL concentration in cerebrospinal fluid).¹⁹

3.5. Prognosis and prognostic factors

The natural course of the disease is characterized by very high variability, depending on many factors. Studies have shown that untreated patients with MS generally reach a substantial level of disability after several years of disease progression. 15-40% of patients experience a mild form of MS. The average life expectancy following the appearance of initial symptoms is approximately 30–40 years. Mortality rates are elevated in the MS population relative to the general population, especially among patients with advanced disability. The leading causes of death are usually secondary complications, including infections and comorbid disorders.⁴¹ The Expanded Disability Status Scale (EDSS) is widely used to assess the performance of patients with multiple sclerosis and is considered a well-defined scale. It was developed based on the Disability Status Scale (DSS) from 1954. The EDSS was introduced in 1983 and is based on a physician's interview and neurological examination, assesses the functioning of eight functional systems (pyramidal, cerebellar, brainstem, sensory, sphincter, visual, mental, and other). The EDSS consists of 20 steps in increments of 0.5. "0" indicates a normal neurological examination, while "10" indicates death due to MS, the score increases as MS worsens.⁴² This scale is also used in studies to assess the influence of prognostic factors on the course

of the disease. Prognostic factors in multiple sclerosis can be divided into four main groups: demographic, clinical, neuroimaging and laboratory factors.⁴¹ Demographic factors that improve prognosis include primarily patient age and gender.⁴³ The influence of gender on the course of the disease is less certain compared to the influence of age. Women are more likely to develop MS, but some studies indicate that men are at greater risk of more rapid disease progression and more rapid progression to higher-level disability. However, in some studies, gender has no impact on the course of the disease.⁴¹ A younger age at onset is associated with a lower risk of developing SMPS, particularly in women. Furthermore, a higher age at onset is associated with a higher risk of achieving an irreversible EDSS score of 6.0 in a shorter time. Although some data do not support gender differences, a significant number of meta-analyses have shown a higher risk of men achieving EDSS 6.0 and 7.0, while female gender has been shown to provide protection against the risk of disability worsening over 12 months. Younger women and a higher EDSS at the time of relapse are considered factors that increase the chance of EDSS improvement after relapse treatment.⁴³ Ethnicity is also a demographic factor that influences the course of the disease. Caucasian patients have a lower risk of developing disability more quickly than African American, Hispanic and Latino patients, but this may be due to their often better access to healthcare.⁴¹ Among clinical factors, the occurrence of mild symptoms at the onset of the disease (sensory symptoms, retrobulbar optic neuritis) compared to the onset of motor and brainstem/cerebral/cerebellar symptoms improves the prognosis. It should be added that visual symptoms, as the first symptoms of the disease, occur more often in women and in younger patients.⁴⁴ Incomplete recovery after the first attack, frequent relapses within the first two years after onset and persistence of clinical and radiological activity despite disease-modifying therapy are also negative prognostic factors.^{41,43} A negative prognosis for the disease also includes a multi-symptom onset of the disease and poses a risk of progression to SMPS. PPMS is consistently recognized as one of the strongest negative prognostic factors and is associated with a faster progression of disability compared to the relapsing-remitting form.⁴¹ Prognosis can also be determined using neuroimaging (radiological prognostic factors). In MS, magnetic resonance imaging (MRI) is the basis for diagnosis. Poor prognosis is posed by a large number of MRI lesions in the early stages of the disease (especially more than 10) and the location of lesions infratentorially, primarily in the brainstem and spinal cord. Persistent contrast activity on MRI during the first months of treatment also indicates the risk of further disease activity and treatment failure. The presence of new spinal cord lesions has also been shown to correlate with the risk of relapse within three months.^{41,43} Among the laboratory factors, the most important is the presence of oligoclonal bands (OCB) in the cerebrospinal fluid (CSF). Detection of CSF bands is associated with an increased risk of transformation from clinically isolated MS to full MS, disease progression, conversion to SPMS, and earlier disability.⁴¹ Promising laboratory markers detected in serum include neurofilament light

chains (NfL) and glial fibrillary acidic protein (GFAP). Increased NfL may correlate with a higher risk of MS relapse, worsening of the EDSS score over the following years, and increased GFAP with more rapid gray matter loss, which may indicate the development of disability independent of relapses and increased SEL (slowly evolving lesions).⁴³ At the time of diagnosis, the choice of therapy is crucial for patient prognosis.⁴¹ The prognosis for MS has been significantly improved by the introduction of DMTs. Studies show that the earlier treatment is initiated, the lower the risk of relapses, the slower progression of disability, and the lower mortality rate. DMT treatment from the time of diagnosis has also been shown to have a positive impact compared to escalation to DMT.⁴³ Currently, due to the use of treatment in patients from the moment of diagnosis, including the introduction of DMT, but also the improvement of diagnostic methods, including the availability of neuroimaging, the life expectancy of patients with MS is shorter by approximately 7 years compared to the general population. Mortality is expected to continue to decline as more patients are successfully treated from the onset of the disease each year, which is the subject of ongoing research.⁴⁵ Multidisciplinary healthcare, including treatment of comorbidities, also improves disease prognosis. There is also evidence that improving lifestyle quality, including physical activity, quitting smoking, and maintaining a healthy body weight, also has a positive impact.^{44,46} Physical exercise, ideally 4-5 sessions of aerobic exercise per week, is a factor that positively influences prognosis. However, prolonged exercise should be avoided, as this can increase neuronal damage.¹⁹

4. Discussion

The findings presented in this review of scientific studies indicate a significant research gap in understanding of the epidemiology, treatment and wide-ranging implications of coping with MS. Further research should focus on a more comprehensive investigation of both the direction and the nature of the association between MS and the presence of mental health disorders. Within the currently available empirical literature, relatively little attention has been devoted to investigating the relationship between the course of multiple sclerosis and the substantial deterioration in sexual functioning experienced by affected individuals. A better understanding of the underlying mechanisms and the identification of potential preventive strategies, in this important area of inquiry, could provide valuable knowledge which might directly influence patients' everyday lives.

5. Conclusions

Despite the development of increasingly advanced and widely available methods for the detection of multiple sclerosis, the diagnosis of this condition continues to rely primarily on Magnetic Resonance Imaging, which remains the gold standard in this regard. The broad spectrum of clinical manifestations associated with the disease not only complicates fast and accurate diagnosis but also poses significant challenges for the therapeutic process itself.

The foregoing review demonstrates that, to achieve satisfactory outcomes and maintain an optimal level of functioning among patients, multiple sclerosis should be approached not merely as an autoimmune demyelinating disorder, but also as a neurodegenerative condition whose manifestations extend beyond the nervous system. Given the unpredictable nature of the disease course and the inability to foresee the clinical consequences of subsequent relapses, the implementation of immunomodulatory and anti-inflammatory therapies has frequently resulted in measurable progress in the management of multiple sclerosis.

Innovative approaches described in recent scientific literature, such as Chimeric Antigen Receptor T-cell (CAR-T) therapy, are based on the restoration and targeted modification of patients' T lymphocytes to selectively eliminate immune cells involved in the demyelinating process, including autoreactive B lymphocytes. Considering all the stated challenges and uncertainties related to the etiological factors, MS pathogenesis, and the selection of appropriate therapeutic strategies, it is essential to recognize that individuals affected by multiple sclerosis should be approached holistically, with equal attention given to both their physical and psychological well-being, to provide them comfort and understanding of their frustration and chronic anxiety.

Disclosure

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References

- ¹ Du L, Xi H, Zhang S, Zhou Y, Tao X, Lv Y, Hou X, Yu L. Effects of exercise in people with multiple sclerosis: a systematic review and meta-analysis. *Front Public Health*. 2024;12:1387658. <https://doi.org/10.3389/fpubh.2024.1387658>
- ² Ordoñez-Rodriguez A, Roman P, Rueda-Ruzafa L, Campos-Rios A, Cardona D. Changes in gut microbiota and multiple sclerosis: a systematic review. *Int J Environ Res Public Health*. 2023;20(5):4624. <https://doi.org/10.3390/ijerph20054624>
- ³ Greenfield AL, Hauser SL. B-cell therapy for multiple sclerosis: entering an era. *Ann Neurol*. 2018;83(1):13-26. <https://doi.org/10.1002/ana.25119>
- ⁴ Montalban X, Matthews PM, Simpson A, Petrie JL, Sammon C, Ramagopalan S, Disanto G, Kuhle J. Real-world evaluation of ocrelizumab in multiple sclerosis: a systematic review. *Ann Clin Transl Neurol*. 2023;10(3):302-311. <https://doi.org/10.1002/acn3.51732>
- ⁵ Zakrzewska-Pniewska B, Adamczyk-Sowa M, Broła W, Kalinowska A, Kułakowska A, Losy J, Mirowska-Guzel D, Potemkowski A, Rejdak K, Sarzyńska-Długosz I, Siger M, Zaborski J, Bartosik-Psujek H. Leczenie i postępowanie objawowe w stwardnieniu rozsianym. Rekomendacje Sekcji SM i Neuroimmunologii Polskiego Towarzystwa Neurologicznego. *Pol Przegl Neurol*. 2019;15(4):191-217. <https://doi.org/10.5603/PPN.2019.0033>
- ⁶ Samjoo IA, Drudge C, Walsh S, Tiwari S, Brennan R, Boer I, Häring DA, Klotz L, Adlard N,

- Banhazi J. Comparative efficacy of therapies for relapsing multiple sclerosis: a systematic review and network meta-analysis. *J Comp Eff Res*. 2023;12(7):e230016. <https://doi.org/10.57264/cer-2023-0016>
- 7 Ministry of Health (Poland). Chorobowość stwardnienia rozsianego w Polsce [Internet]. Warsaw (Poland): Ministry of Health; [cited 2026 Jun 11]. Available from: https://analizy.mz.gov.pl/html/zpa_sm/chorobowosc.html
- 8 Hollenbach JA, Oksenberg JR. The immunogenetics of multiple sclerosis: a comprehensive review. *J Autoimmun*. 2015;64:13-25. <https://doi.org/10.1016/j.jaut.2015.06.010>
9. Handel AE, Williamson AJ, Disanto G, Handunnetthi L, Giovannoni G, Ramagopalan SV. An updated meta-analysis of risk of multiple sclerosis following infectious mononucleosis. *PLoS One*. 2010;5(9):e12496. <https://doi.org/10.1371/journal.pone.0012496>
- 10 Lang HLE, Jacobsen H, Ikemizu S, Andersson C, Harlos K, Madsen L, Hjorth P, Søndergaard L, Svejgaard A, Wucherpfennig KW, Stuart DI, Bell JI, Jones EY, Fugger L. A functional and structural basis for TCR cross-reactivity in multiple sclerosis. *Nat Immunol*. 2002;3(10):940-943. <https://doi.org/10.1038/ni835>
- 11 Tracy SI, Kakalacheva K, Lünemann JD, Luzuriaga K, Middeldorp J, Thorley-Lawson DA. Persistence of Epstein-Barr virus in self-reactive memory B cells. *J Virol*. 2012;86(22):12330-12340. <https://doi.org/10.1128/JVI.01699-12>
- 12 Giovannoni G, Cutter G, Sormani MP, Belachew S, Hyde R, Koendgen H, Knappertz V, Tomic D, Leppert D, Herndon R, Wheeler-Kingshott CAM, Ciccarelli O, Selwood D, Verdun di Cantogno E, Ben-Amor AF, Matthews P, Carassiti D, Baker D, Schmierer K. Is multiple sclerosis a length-dependent central axonopathy? The case for therapeutic lag and the asynchronous progressive MS hypotheses. *Mult Scler Relat Disord*. 2017;12:70-78. <https://doi.org/10.1016/j.msard.2017.01.007>
13. Pearce JMS. Historical descriptions of multiple sclerosis. *Eur Neurol*. 2005;54(1):49-53. <https://doi.org/10.1159/000087387>
- 14 Karussis D. The diagnosis of multiple sclerosis and the various related demyelinating syndromes: a critical review. *J Autoimmun*. 2014;48-49:134-142. <https://doi.org/10.1016/j.jaut.2014.01.022>
- 15 Lassmann H. Pathology and disease mechanisms in different stages of multiple sclerosis. *J Neurol Sci*. 2013;333(1-2):1-4. <https://doi.org/10.1016/j.jns.2013.05.010>
- 16 Trapp BD, Peterson J, Ransohoff RM, Rudick R, Mörk S, Bö L. Axonal transection in the lesions of multiple sclerosis. *N Engl J Med*. 1998;338(5):278-285. <https://doi.org/10.1056/NEJM199801293380502>
- 17 Prineas JW, Kwon EE, Cho ES, Sharer LR, Barnett MH, Oleszak EL, Hoffman B, Morgan BP. Immunopathology of secondary-progressive multiple sclerosis. *Ann Neurol*. 2001;50(5):646-657. <https://doi.org/10.1002/ana.1255>

- 18 Correale J, Gaitán MI, Ysraelit MC, Fiol MP. Progressive multiple sclerosis: from pathogenic mechanisms to treatment. *Brain*. 2017;140(3):527-546. <https://doi.org/10.1093/brain/aww258>
- 19 Dobson R, Giovannoni G. Multiple sclerosis - a review. *Eur J Neurol*. 2019;26(1):27-40. <https://doi.org/10.1111/ene.13819>
- 20 Ghasemi N, Razavi S, Nikzad E. Multiple sclerosis: pathogenesis, symptoms, diagnoses and cell-based therapy. *Cell J*. 2017;19(1):1-10. <https://doi.org/10.22074/cellj.2016.4867>
- 21 Oliva Ramirez A, Keenan A, Kalau O, Worthington E, Cohen L, Singh S. Prevalence and burden of multiple sclerosis-related fatigue: a systematic literature review. *BMC Neurol*. 2021;21(1):468. <https://doi.org/10.1186/s12883-021-02396-1>
- 22 Olek MJ, Howard J. Evaluation and diagnosis of multiple sclerosis in adults. In: UpToDate. Waltham (MA): UpToDate Inc. Accessed 2026 Jun 7. Available from: <https://www.uptodate.com/contents/evaluation-and-diagnosis-of-multiple-sclerosis-in-adults>
- 23 Shah P. Symptomatic management in multiple sclerosis. *Ann Indian Acad Neurol*. 2015;18(Suppl 1):S35-S42. <https://doi.org/10.4103/0972-2327.164827>
- 24 Chwastiak LA, Ehde DM. Psychiatric issues in multiple sclerosis. *Psychiatr Clin North Am*. 2007;30(4):803-817. <https://doi.org/10.1016/j.psc.2007.07.003>
- 25 Ford H. Clinical presentation and diagnosis of multiple sclerosis. *Clin Med (Lond)*. 2020;20(4):380-383. <https://doi.org/10.7861/clinmed.2020-0292>
- 26 Boski N, Gulati V, Raj R, Gulati P. Multiple sclerosis-minimizing errors in radiological diagnosis. *Neurol India*. 2021;69(6):1539-1546. <https://doi.org/10.4103/0028-3886.333497>
- 27 Okuda DT, Siva A, Kantarci O, Inglese M, Katz I, Tutuncu M, Keegan BM, Donlon S, Hua LH, Vidal-Jordana A, Montalban X, Rovira A, Tintoré M, Amato MP, Brochet B, de Seze J, Brassat D, Vermersch P, De Stefano N, Sormani MP, Pelletier D, Lebrun C, Radiologically Isolated Syndrome Consortium (RISC), Club Francophone de la Sclérose en Plaques (CFSEP). Radiologically isolated syndrome: 5-year risk for an initial clinical event. *PLoS One*. 2014;9(3):e90509. <https://doi.org/10.1371/journal.pone.0090509>
- 28 Cohen JA. 2024 revision of the McDonald diagnostic criteria for MS: substantial and substantive changes. *Mult Scler*. 2025;31(11):1269-1275. <https://doi.org/10.1177/13524585251351860>
- 29 Brownlee WJ, Maccarrone D, Nistri R, Yam C, Wilson H, Wright S, et al. Performance of the 2024 McDonald Criteria in patients under evaluation for suspected multiple sclerosis. *Neurology*. 2026;106(6):e214688. <https://doi.org/10.1212/WNL.0000000000214688>
- 30 European Medicines Agency. Tysabri (natalizumab): summary of product characteristics [Internet]. 2026 [cited 2026 Jun 3]. Available from: <https://www.ema.europa.eu/en/medicines/human/EPAR/tysabri>
- 31 European Medicines Agency. Gilenya (fingolimod): summary of product characteristics

[Internet]. 2026 [cited 2026 Jun 3]. Available from:

<https://www.ema.europa.eu/en/medicines/human/EPAR/gilenya>

32 European Medicines Agency. Ocrevus (ocrelizumab): summary of product characteristics

[Internet]. 2025 [cited 2026 Jun 3]. Available from:

<https://www.ema.europa.eu/en/medicines/human/EPAR/ocrevus>

33 European Medicines Agency. Avonex (interferon beta-1a): summary of product characteristics

[Internet]. [cited 2026 Jun 4]. Available from:

<https://www.ema.europa.eu/en/medicines/human/EPAR/avonex>

34 Teva Pharmaceuticals Europe B.V. Copaxone (glatiramer acetate): summary of product characteristics [Internet]: Teva Pharmaceuticals Europe B.V.; [cited 2026 Jun 3]. Available from:

<https://www.medicines.org.uk/emc/product/7046/smpc#gref>

35 European Medicines Agency. Aubagio (teriflunomide): summary of product characteristics

[Internet]. [cited 2026 Jun 3]. Available from:

<https://www.ema.europa.eu/en/medicines/human/EPAR/aubagio>

36 European Medicines Agency. Lemtrada (alemtuzumab): summary of product characteristics

[Internet]. [cited 2026 Jun 3]. Available from:

<https://www.ema.europa.eu/en/medicines/human/EPAR/lemtrada>

37 European Medicines Agency. Mavenclad (cladribine): summary of product characteristics

[Internet]. [cited 2026 Jun 3]. Available from:

<https://www.ema.europa.eu/en/medicines/human/EPAR/mavenclad>

38 Fischbach F, Richter J, Pfeffer LK, Fehse B, Berger SC, Reinhardt S, Kuhle J, Badbaran A, Rathje K, Gagelmann N, Borie D, Seibel J, Ayuk F, Friese MA, Heesen C, Kröger N. CD19-targeted chimeric antigen receptor T cell therapy in two patients with multiple sclerosis. *Med (N Y)*. 2024;5(6):550-558.e2. <https://doi.org/10.1016/j.medj.2024.03.002>

39 Ortuño-Sahagún D, Hermosillo-Abundis C, Reyes-Mata MP, Arias Carrión Ó. CAR T cells for multiple sclerosis: engineering T cells to disrupt chronic B cell-driven neuroinflammation. *Mult Scler Relat Disord*. 2025;104:106812. <https://doi.org/10.1016/j.msard.2025.106812>

40. Konitsioti AM, Prüss H, Laurent S, Fink GR, Heesen C, Warnke C. Chimeric antigen receptor T-cell therapy for autoimmune diseases of the central nervous system: a systematic literature review. *J Neurol*. 2024;271(10):6526-6542. <https://doi.org/10.1007/s00415-024-12642-4>

41 Maciejowska-Szydło K, Puz P. Early prognostic factors in multiple sclerosis: clinical and therapeutic implications. *Medicina (Kaunas)*. 2026;62(3):475.

<https://doi.org/10.3390/medicina62030475>

42 Çinar BP, Yorgun YG. What we learned from the history of multiple sclerosis measurement: Expanded Disability Status Scale. *Noro Psikiyatrs Ars*. 2018;55(Suppl 1):S69-S75.

<https://doi.org/10.29399/npa.23343>

43 Guerra T, Copetti M, Achille M, Ferri C, Simone M, D'Alfonso S, et al. Refining prognostic factors in adult-onset multiple sclerosis: a narrative review of current insights. *Int J Mol Sci*. 2025;26(16):7756. <https://doi.org/10.3390/ijms26167756>

44 Hedström AK, Olsson T, Alfredsson L. Determinants and prognostic value of onset symptoms in multiple sclerosis. *J Neurol*. 2025;273(1):2. <https://doi.org/10.1007/s00415-025-13536-9>

45 Kuutti K, Laakso SM, Viitala M, Atula S, Soilu-Hänninen M. Mortality and causes of death for people with multiple sclerosis: a Finnish nationwide register study. *J Neurol*. 2025;272(5):370. <https://doi.org/10.1007/s00415-025-13112-1>

46 Tafti D, Ehsan M, Xixis KL. Multiple sclerosis. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 [updated 2024 Mar 20]. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK499849/>