Journal of Population Therapeutics & Clinical Pharmacology

RESEARCH ARTICLE
DOI: 10.53555/jptcp.v30i17.5823

OVERVIEW OF MULTIPLE SCLEROSIS

Alaa Ali Ahmad Al-Dawani[1], Hussain Ali A Albakhite[2], Ruoa Faisal Albunayyan[3], Turki Musleh Muhia Almutiri[4], Lama Zaki Al Nasrallah[5], Suzan Talal Aljehani[6], Sultan Surur Saleem Alrashidi[7], Mansour Awadh Allah Althobaiti[8], Faisal Mohammad Mohsen Alotaibi[9], Mohammed Musayfir Musaynid Aljuaid[10], Nawaf Mohammed Alamri[11], Saleh Mohammed Shami[12],Salman Awadh Alraddadi[13], Mariam Eid Alanzi[14]

[1*]Maternity And Children Hospital – Dammam – Saudi Arabia
[2]Prince Saud Bin Jalawi Hospital - Al Ahsa – Saudi Arabia
[3]Security Forces Hospital – Makkah – Saudi Arabia
[4,8,10,11]King Faisal Medical Complex - Taif – Saudi Arabia
[5]Imam Abdulrahman Alfaisal Hospital – Riyadh – Saudi Arabia
[6]Alamal Mental Health – Medina – Saudi Arabia
[7,14]King Salman Bin Abdulaziz Medical City – Medina – Saudi Arabia
[9]Directorate Of Health Affairs – Taif – Saudi Arabia
[12]Eradah and Mental Health Complex – Jeddah – Saudi Arabia
[13]Health administration in Directorate of Health Affairs - Madina - Saudi Arabia

***Corresponding Author:** Alaa Ali Ahmad Al-Dawani
*Maternity And Children Hospital – Dammam – Saudi Arabia

Abstract:
Multiple sclerosis (MS) is a chronic inflammatory disease affecting the central nervous system (CNS), characterized by immune-mediated assaults on the myelin sheath. This autoimmune disorder primarily impacts young individuals and can result in permanent axonal degeneration. The manifestations of MS vary, encompassing relapsing-remitting MS, primary-progressive MS, and secondary-progressive MS. The etiology of the disease stems from an immune system dysfunction, culminating in the obliteration of healthy nervous system cells. Therapeutic approaches for MS are geared towards averting exacerbations and protracted functional deterioration, with diverse FDA-endorsed drugs stratified according to their efficacy in relapse mitigation. The precise origin of MS remains elusive; nonetheless, immunomodulated genetic predisposition and environmental factors are postulated to exert considerable influence on its onset.

Introduction:
Multiple sclerosis (MS) is a chronic inflammatory disease of the central nervous system (CNS) characterized by myelin degradation, axonal degeneration, and neuronal loss. [1]The pathophysiology of MS involves numerous cellular mechanisms related to autoimmunity, which contribute to the progression of the disease. Inflammatory processes in the brain and spinal cord destroy myelin, impairing nerve function. [2]. Besides, Risk factors for MS include age, sex, genetics, environment, smoking, injuries, and infections. [3]. The disease is more prevalent in women and commonly occurs in Europe and America. In addition, the immune system's adaptive and innate arms are implicated in developing MS lesions. CD4+ and CD8+ T cells and B cells are found in active MS lesions and contribute to the inflammatory response. Aberrant lymphocyte activity, particularly Th1 and Th17

populations, is associated with MS pathogenesis. B cells also produce antibodies against myelin basic protein, further contributing to neuronal damage. In addition, myeloid cells, such as macrophages and microglia, play a role in myelin and neuronal injury during MS. Also, Epigenetic changes, including DNA methylation, histone modifications, and microRNA-associated gene silencing, play a crucial role in MS development and progression. [4].

Nevertheless, compartmentalized inflammation and its effector mechanisms, such as pyroptosis, are strongly associated with MS severity [5]. In addition, DNA methylation, specifically at CpG dinucleotides, is a central epigenetic mechanism that can modulate gene expression in MS [6]. Furthermore, non-synonymous single-nucleotide polymorphisms (nsSNPs) in MS-related genes can affect protein structure and function, potentially contributing to disease pathogenesis [7]. Variants in the superoxide dismutase 1 (SOD1) gene, a known cause of ALS, exhibit structural and dynamic differences that influence ALS patients' clinical phenotype and survival time. Environmental risk factors such as infections, vaccinations, nutritional habits, hormonal factors, and physical and chemical agents have also been implicated in MS pathogenesis [8]. In addition, There is evidence of gene-environment interactions, with a high burden of autosomal genetic risk interacting with environmental risk factors such as childhood obesity and smoking to increase the risk of MS [9]. Additionally, certain environmental factors, such as tobacco smoking, low vitamin D levels, and Epstein Barr Virus (EBV) seropositivity, have been associated with an increased risk of developing MS [10]. In addition, Axonal damage is a key component of disease progression and disability in MS [11]. Extensive research has focused on quantifying neurofilament light chain (NfL), a biomarker of axonal damage, in MS patients [12]. Studies have shown that axonal damage is most pronounced in early, actively demyelinating MS lesions. Serum NfL levels have been found to correlate with acute signs of inflammation and can predict disease activity and severity [13]. Advanced technologies such as Single Molecular Array (Simoa) have improved the sensitivity and accuracy of NfL quantification, making it valuable in clinical settings. Besides, Axonal damage in MS is believed to be caused by a combination of immune reactions, oxidative stress, and mitochondrial dysfunction. Immune cells, such as T and B cells, can cause demyelination or axonal/neuronal damage [14]. Chronic inflammation and microglial cell activation contribute to axonal and neuronal damage [12]. Oxidative stress, which leads to tissue injury, is a key factor in neurodegenerative disorders like MS [15]. Axonal mitochondria, which provide energy for axons and neurons, are particularly vulnerable to oxidative injury [16]. Impaired axo-glial communication, resulting from axonal mitochondrial dysfunction, can affect axonal integrity and signaling [17]. These mechanisms and a variably primed immune system may lead to the development of MS and its different subtypes. Nevertheless, Blood-brain barrier (BBB) dysfunction in (MS) is caused by various mechanisms. One mechanism involves the alteration of tight junction proteins, such as claudin-5, responsible for sealing the intercellular space of endothelial cells in the BBB [18]. Another mechanism involves the role of repulsive guidance molecule-a (RGMa) in regulating BBB permeability. RGMa, along with its signaling counterpart bone morphogenetic protein 2 (BMP2)/bone morphogenetic protein receptor type II (BMPRII), is increased in MS and leads to the breakdown of the BBB [19]. Additionally, intrinsic impairments in BBB function have been observed in MS patients, including impaired junctional integrity, barrier properties, and efflux pump activity [20]. Activation of Wnt/β-catenin signaling has been shown to enhance barrier characteristics and reduce the inflammatory phenotype in MS-derived endothelial progenitor cells [21]. In addition, Endothelial-to-mesenchymal transition (EndMT) is associated with BBB dysfunction in MS, contributing to vessel instability and barrier disruption [22].

Manifestations:

MS can have physical and psychological manifestations. That includes numbness, facial paralysis, difficulty chewing, and blurred vision. [23]. MS can also lead to cranial nerve paralysis, affecting facial and extremities nerves. [24]. Psychiatric manifestations of MS can include major depression, bipolar disorder, psychosis, anxiety, insomnia, personality changes, cognitive impairment, pseudobulbar affect, and substance use disorders. [25]. Also, Hypoxia and inflammation have been identified as key factors in the progression of MS, suggesting a "hypoxia-inflammation cycle" that

plays a role in disease progression. [26]. Nevertheless, Bladder and bowel dysfunction are common symptoms in people with MS and can significantly impact their quality of life. Studies have shown that these symptoms are more prevalent in MS patients with higher disability levels and longer disease duration. [27]. Besides, Speech and swallowing difficulties are common in individuals with MS. Cognitive-linguistic symptoms, such as word-finding difficulties and getting off-topic, are frequently reported about communication [28]. Regarding specific speech-related symptoms, self-reported problems include speech-related fatigue and imprecise articulation. In addition, Dysphagia in MS patients is associated with increased symptoms of psychological stress and decreased use of cognitive reappraisal strategies. Additionally, dysphagia is more common in progressive MS courses and is related to cerebellar impairment and motor dysfunction. Overall, dysphagia and speech difficulties in MS highlight the need for improved access to speech and language pathology services to address these symptoms and improve overall functioning and quality of life. Also, Heat sensitivity in (MS) may be related to central nervous system conduction deficits and autonomic dysfunction [29]. However, objective measurement of autonomic and corticospinal integrity did not contribute to heat sensitivity in MS. [30]. In addition, Lack of disease-modifying therapy (DMT) use and self-reported difficulty using hands in everyday tasks were strongly associated with heat sensitivity in MS. [31]. Nevertheless, Thermoregulatory responses to exercise seem to be preserved in MS, suggesting that altered thermoregulation is unlikely to be the cause of reduced distance achieved during exercise tests. Heat-sensitive individuals with MS may exhibit thermosensory abnormalities, including threshold variations and sensitivity to temperature stimuli. Anomalously warm weather is associated with an increased risk of emergency department and inpatient visits for MS-related issues.

Diagnosis:

The current diagnostic criteria for MS are the MacDonald 2017 criteria, which allow for a safer and earlier diagnosis and minimize the risk of overdiagnosis [32]. Besides, Techniques such as spectral-domain optical coherence tomography (OCT) have been used to identify new biomarkers for the early diagnosis of MS [33]. Also, Image pre-processing steps, including skull stripping and lesion segmentation, are critical in the development of computer-aided differential diagnosis tools for MS [34]. Additionally, blood and cerebrospinal fluid (CSF) oxidative stress markers have been evaluated in subjects with MS, but non-invasive imaging techniques offer real-time assessment within the brain. Overall, the use of imaging techniques, along with clinical and biological findings, plays a crucial role in the diagnostic process for MS. Nevertheless, Evoked potentials, specifically visual evoked potentials (VEPs) and motor evoked potentials (MEPs), can provide insights into the underlying neural mechanisms of MS and guide the development of new therapies. VEPs can assess neurophysiological dysfunction in the visual pathway, which is important for MS diagnosis and preclinical models. [35]. MEPs, on the other hand, can serve as a biomarker to assess pathological processes in MS patients that are unseen with conventional imaging. [36].

Treatment:

The current treatment options for (MS) include disease-modifying therapies (DMTs) that target the inflammatory component of the disease and aim to reduce relapse frequency and disability progression [37]. There are 19 FDA-approved immunotherapies available in 2021, each with different mechanisms of action, routes of administration, efficacy, safety, and tolerability profiles [38]. These therapies have shown effectiveness in reducing relapse frequency and accumulation of neurologic disability in MS patients [39]. In addition to DMTs, emerging therapies such as CNS-penetrant Bruton's tyrosine kinase inhibitors and autologous hematopoietic stem cell transplantation are being explored. The management of MS also involves a multidisciplinary approach to address symptoms and disability, requiring the participation of various healthcare professionals and the active involvement of the patient. It is important to comprehensively understand the available therapies' characteristics, indications, safety, and efficacy profiles to tailor the treatment strategy to individual patient characteristics. In addition, The most effective treatments for MS in terms of disease progression include monoclonal antibody (mAb) therapies such as alemtuzumab, ofatumumab, and

rituximab [40]. Other effective treatments include natalizumab and fingolimod [41]. These therapies have shown superior efficacy in reducing relapses and disability worsening compared to other disease-modifying therapies (DMTs) like dimethyl fumarate, teriflunomide, glatiramer acetate, and interferon beta [42]. Additionally, newer therapies like ozanimod, ponesimod, and rituximab have also shown promise in reducing relapse rates. It is important to note that the effectiveness of DMTs can vary depending on the specific outcome measure used, such as annualized relapse rate or disability progression [43]. Also, High-dosage corticosteroids, such as methylprednisolone (MP), are often used to manage acute MS relapses [44]. Corticosteroids can also be used in combination with other MS treatments and during pregnancy and lactation [45]. Nevertheless, Different management approaches for (MS) relapses can have potential side effects and risks. Disease-modifying therapies (DMTs) are commonly used to reduce the frequency of relapses and the risk of disability progression. However, DMTs can have side effects, and their effectiveness may vary depending on the type and stage of MS. High-dose immunosuppressive therapy with autologous hematopoietic stem cell transplantation (HDIT/AHSCT) is a promising method for treating MS. Still, it carries the risk of serious complications. The frequency and severity of adverse effects from HDIT/AHSCT have decreased over time due to improvements in treatment protocols and patient selection. Thorough monitoring and patient education are essential for managing the potential side effects of MS therapies [46].

References:

1. Dighriri IM, Aldalbahi AA, Albeladi F, et al.: An overview of the history, pathophysiology, and pharmacological interventions of multiple sclerosis. Cureus. 2023, 15.
2. Patejdl R, Zettl UK: The pathophysiology of motor fatigue and fatigability in multiple sclerosis. Frontiers in Neurology. 2022, 13. 10.3389/fneur.2022.891415
3. Kee R, Naughton M, McDonnell GV, Howell OW, Fitzgerald DC: A Review of Compartmentalised Inflammation and Tertiary Lymphoid Structures in the Pathophysiology of Multiple Sclerosis. Biomedicines. 2022, 10:2604.
4. Eslahi M, Nematbakhsh N, Dastmalchi N, Teimourian S, Safaralizadeh R: An Updated Review of Epigenetic-Related Mechanisms and their Contribution to Multiple Sclerosis Disease. CNS & Neurological Disorders-Drug Targets (Formerly Current Drug Targets-CNS & Neurological Disorders). 2023, 22:381-393.
5. Kiselev IS, Kulakova OG, Boyko AN, Favorova OO: DNA Methylation As an Epigenetic Mechanism in the Development of Multiple Sclerosis. Acta Naturae. 2021, 13:45-57. 10.32607/actanaturae.11043
6. Erkal B, Akçeşme B, Çoban A, Korkut Ş V: A comprehensive in silico analysis of multiple sclerosis related non-synonymous SNPs and their potential effects on protein structure and function. Mult Scler Relat Disord. 2022, 68:104253. 10.1016/j.msard.2022.104253
7. Kalia M, Miotto M, Ness D, et al.: Molecular dynamics analysis of superoxide dismutase 1 mutations suggests decoupling between mechanisms underlying ALS onset and progression. Comput Struct Biotechnol J. 2023, 21:5296-5308. 10.1016/j.csbj.2023.09.016
8. Jacobs BM, Noyce AJ, Bestwick J, Belete D, Giovannoni G, Dobson R: Gene-Environment Interactions in Multiple Sclerosis: A UK Biobank Study. Neurol Neuroimmunol Neuroinflamm. 2021, 8. 10.1212/nxi.0000000000001007
9. Omar D, Sawsan S, Afnan A: Exploring the Effect of Genetic, Environmental and Lifestyle Factors on Multiple Sclerosis Susceptibility. Multiple Sclerosis. Uday K, Abhishek S (eds): IntechOpen, Rijeka; 2022. Ch. 3. 10.5772/intechopen.105834
10. Zarghami A, Li Y, Claflin SB, van der Mei I, Taylor BV: Role of environmental factors in multiple sclerosis. Expert Rev Neurother. 2021, 21:1389-1408. 10.1080/14737175.2021.1978843
11. Pafiti A, Krashias G, Tzartos J, et al.: A Comparison of Two Analytical Approaches for the Quantification of Neurofilament Light Chain, a Biomarker of Axonal Damage in Multiple Sclerosis. Int J Mol Sci. 2023, 24. 10.3390/ijms241310787
12. Mey GM, Mahajan KR, DeSilva TM: Neurodegeneration in multiple sclerosis. WIREs Mech Dis. 2023, 15:e1583. 10.1002/wsbm.1583

13. Steffen F, Uphaus T, Ripfel N, et al.: Serum Neurofilament Identifies Patients With Multiple Sclerosis With Severe Focal Axonal Damage in a 6-Year Longitudinal Cohort. Neurol Neuroimmunol Neuroinflamm. 2023, 10. 10.1212/nxi.0000000000200055
14. Bitsch A, Schuchardt J, Bunkowski S, Kuhlmann T, Brück W: Acute axonal injury in multiple sclerosis. Correlation with demyelination and inflammation. Brain. 2000, 123 (Pt 6):1174-1183. 10.1093/brain/123.6.1174
15. Eliseeva DD, Zakharova MN: [Mechanisms of Neurodegeneration in Multiple Sclerosis]. Zh Nevrol Psikhiatr Im S S Korsakova. 2022, 122:5-13. 10.17116/jnevro20221220725
16. Correale J, Marrodan M, Ysrraelit MC: Mechanisms of Neurodegeneration and Axonal Dysfunction in Progressive Multiple Sclerosis. Biomedicines. 2019, 7. 10.3390/biomedicines7010014
17. Bergaglio T, Luchicchi A, Schenk GJ: Engine Failure in Axo-Myelinic Signaling: A Potential Key Player in the Pathogenesis of Multiple Sclerosis. Front Cell Neurosci. 2021, 15:610295. 10.3389/fncel.2021.610295
18. 18. Angelini G, Bani A, Constantin G, Rossi B: The interplay between T helper cells and brain barriers in the pathogenesis of multiple sclerosis. Front Cell Neurosci. 2023, 17:1101379. 10.3389/fncel.2023.1101379
19. Hoettels BA: Mechanisms for Extracellular Matrix-Dependent Blood-Brain Barrier Dysfunction. Boise State University, 2021.
20. Zhang L, Tang S, Ma Y, et al.: RGMa Participates in the Blood-Brain Barrier Dysfunction Through BMP/BMPR/YAP Signaling in Multiple Sclerosis. Front Immunol. 2022, 13:861486. 10.3389/fimmu.2022.861486
21. Nishihara H, Perriot S, Gastfriend BD, et al.: Intrinsic blood-brain barrier dysfunction contributes to multiple sclerosis pathogenesis. Brain. 2022, 145:4334-4348. 10.1093/brain/awac019
22. Patabendige A, Janigro D: The role of the blood-brain barrier during neurological disease and infection. Biochem Soc Trans. 2023, 51:613-626. 10.1042/bst20220830
23. Khouzam HR: The Psychiatric Manifestations of Multiple Sclerosis and their Treatment. Journal of Spine Research & Reports SRC/JSRR-104 DOI: doi org/1047363/JSRR/2022 (1). 2022, 103.
24. Altun Y, BULUT H, Ali A: Unusual primary manifestations of multiple sclerosis: A case report. Journal of Surgery and Medicine. 2021, 5:575-577.
25. Javalkar V, McGee J, Minagar A: Clinical Manifestations of Multiple Sclerosis. 2016. 1-12. 10.1016/B978-0-12-800763-1.00001-4
26. Yang R, Dunn JF: Multiple sclerosis disease progression: Contributions from a hypoxia-inflammation cycle. Mult Scler. 2019, 25:1715-1718. 10.1177/1352458518791683
27. Alvino B, Arianna F, Assunta B, et al.: Prevalence and predictors of bowel dysfunction in a large multiple sclerosis outpatient population: an Italian multicenter study. J Neurol. 2022, 269:1610-1617. 10.1007/s00415-021-10737-w
28. Johansson K, Schalling E, Hartelius L: Self-Reported Changes in Cognition, Communication and Swallowing in Multiple Sclerosis: Data from the Swedish Multiple Sclerosis Registry and from a National Survey. Folia Phoniatr Logop. 2021, 73:50-62. 10.1159/000505063
29. Critch AL, Snow NJ, Alcock LR, Chaves AR, Buragadda S, Ploughman M: Multiple sclerosis-related heat sensitivity linked to absence of DMT prescription and subjective hand impairment but not autonomic or corticospinal dysfunction. Mult Scler Relat Disord. 2023, 70:104514. 10.1016/j.msard.2023.104514
30. Gervasoni E, Bertoni R, Anastasi D, et al.: Acute Thermoregulatory and Cardiovascular Response to Submaximal Exercise in People With Multiple Sclerosis. Front Immunol. 2022, 13:842269. 10.3389/fimmu.2022.842269
31. Elser H, Parks RM, Moghavem N, et al.: Anomalously warm weather and acute care visits in patients with multiple sclerosis: A retrospective study of privately insured individuals in the US. PLoS Med. 2021, 18:e1003580. 10.1371/journal.pmed.1003580
32. Oh J: Diagnosis of Multiple Sclerosis. Continuum (Minneap Minn). 2022, 28:1006-1024. 10.1212/con.0000000000001156

33. Ortiz M, Mallen V, Boquete L, et al.: Diagnosis of multiple sclerosis using optical coherence tomography supported by artificial intelligence. Mult Scler Relat Disord. 2023, 74:104725. 10.1016/j.msard.2023.104725
34. Hollen C, Neilson LE, Barajas RF, Greenhouse I: Oxidative stress in multiple sclerosis—Emerging imaging techniques. Frontiers in Neurology. 2023, 13:1025659.
35. Marenna S, Rossi E, Huang SC, Castoldi V, Comi G, Leocani L: Visual evoked potentials waveform analysis to measure intracortical damage in a preclinical model of multiple sclerosis. Front Cell Neurosci. 2023, 17:1186110. 10.3389/fncel.2023.1186110
36. Jacques FH, Apedaile BE, Danis I, Sikati-Foko V, Lecompte M, Fortin J: Motor Evoked Potential-A Pilot Study Looking at Reliability and Clinical Correlations in Multiple Sclerosis. J Clin Neurophysiol. 2023. 10.1097/wnp.0000000000001003
37. Maarouf A, Audoin B, Pelletier J: [Current management of multiple sclerosis]. Rev Prat. 2022, 72:399-404.
38. Yang JH, Rempe T, Whitmire N, Dunn-Pirio A, Graves JS: Therapeutic Advances in Multiple Sclerosis. Front Neurol. 2022, 13:824926. 10.3389/fneur.2022.824926
39. Callegari I, Derfuss T, Galli E: Update on treatment in multiple sclerosis. Presse Med. 2021, 50:104068. 10.1016/j.lpm.2021.104068
40. Samjoo IA, Drudge C, Walsh S, et al.: Comparative efficacy of therapies for relapsing multiple sclerosis: a systematic review and network meta-analysis. J Comp Eff Res. 2023, 12:e230016. 10.57264/cer-2023-0016
41. Dimitriou NG, Meuth SG, Martinez-Lapiscina EH, Albrecht P, Menge T: Treatment of Patients with Multiple Sclerosis Transitioning Between Relapsing and Progressive Disease. CNS Drugs. 2023, 37:69-92. 10.1007/s40263-022-00977-3
42. Li H, Lian G, Wang G, Yin Q, Su Z: A review of possible therapies for multiple sclerosis. Mol Cell Biochem. 2021, 476:3261-3270. 10.1007/s11010-021-04119-z
43. Diouf I, Malpas CB, Sharmin S, et al.: Effectiveness of multiple disease-modifying therapies in relapsing-remitting multiple sclerosis: causal inference to emulate a multiarm randomised trial. J Neurol Neurosurg Psychiatry. 2023, 94:1004-1011. 10.1136/jnnp-2023-331499
44. Fischer HJ, Finck TLK, Pellkofer HL, Reichardt HM, Lühder F: Glucocorticoid Therapy of Multiple Sclerosis Patients Induces Anti-inflammatory Polarization and Increased Chemotaxis of Monocytes. Front Immunol. 2019, 10:1200. 10.3389/fimmu.2019.01200
45. Hoepner R, Chan AH-K: mTOR Inhibitor-Corticoid Combination Therapy For Multiple Sclerosis. 2018.
46. Al Malik YM, Al Thubaiti IA, AlAmmari MA, et al.: Saudi Consensus Recommendations on the Management of Multiple Sclerosis: Disease-Modifying Therapies and Management of Relapses. Clinical and Translational Neuroscience. 2022, 6:27.