Minireview Article

A Review Study of Multiple Sclerosis (MS) - Axonal Demyelination Leading To Neurologic Impairment

ABSTRACT

Introduction: Multiple Sclerosis (MS) is a central nervous system auto-immune condition signaled and marked by inflammatory action which leads primarily to demyelination resulting in neurologic impairments. This condition is more common in genetically-disposed individuals and individuals who have had a history of Epstein–Barr virus (EBV) infection

Aim: The study's aim is to examine recent knowledge on the etiology and clinical manifestations of multiple sclerosis, as well as diagnostic testing and recent management options that are being explored to improve the living conditions of people living with Multiple Sclerosis..

Method: This review article focuses on research studies that have relevant, up-to-date and current therapies employed in the management of individuals living with Multiple Sclerosis. It also includes research studies that take a look at Multiple Sclerosis from the viewpoint of the caretaker

Results: In this review, it can be seen that the most common clinical manifestation include cognitive impairment, fatigue, psychiatric impairments. The prevalence of Multiple Sclerosis is closely associated with a history of Epstein–Barr virus (EBV) infection as well as genetic predisposition. Pharmacological therapy has been proven to reduce the incidents of a major relapse but hasn't been advised for patients with a mild relapse. Physical therapy has been proven to be effective when individualized but this is not cost-effective. It has been advised for patients with a mild relapse and for patients undergoing pharmacological therapy, however there is a drawback – physical of therapy can only be administered by very qualified professionals and there is a scarcity of these professionals.

Conclusion: Physical Therapy in conjunction with pharmacological therapy, with further improvements, can drastically improve the quality of lives for people living with Multiple Sclerosis

Comment [h1]: There have been no details in article regarding this

Comment [h2]:

Keywords: Multiple Sclerosis; Demyelination; Inflammation; Neurologic impairments; Epstein–Barr virus (EBV)

1. INTRODUCTION

Multiple Sclerosis (MS) is a central nervous system auto-immune condition signaled and marked by inflammatory action which leads primarily to demyelination resulting in neurologic impairments [1]. Axonal injury and neuronal death are a result of inflammation. These phenomena are widely known to occur early in the disease, as well as later on, and these serve as the foundation of permanent physical and cognitive

impairment [2]. Multiple sclerosis is a complex illness in which several genes, as well as several well-defined environmental factors including but not limited to vitamin D or ultraviolet B light (UVB) exposure, Epstein–Barr virus (EBV) infection, obesity, and smoking, all play a role in disease susceptibility.[3].

Individuals with MS often have a clinically isolated syndrome (CIS). This syndrome is described as a one-of-a-kind first neurological event largely defined by demyelination of the optic nerve and almost every component of the brain [4].

MS has been divided into several clinical and pathological subgroups. Broadly, attacks (relapses) occur in around 80–85% of patients, with full or partial remissions following them, whereas 10–15% of patients have a gradual, progressive course with no relapses.

2. CAUSES OF MULTIPLE SCLEROSIS

Multiple Sclerosis does not appear to be caused by a single agent; rather, As a result of exposure to environmental stimuli, it appears in genetically susceptible populations. [5]. The causes can be broadly classified under two main groups:

2.1 Genetic Factors:

Although different hypotheses have been presented, the purported "outside-in" mechanism involves CD4+ proinflammatory T cells. According to the researchers, an unknown antigen stimulates and activates the myelin-specific T cells; Th1 and Th17, resulting in CNS endothelium attachment, blood-brain barrier bridging, and subsequent immunological assault via cross-reactivity. The "inside-out" theory proposes that inflammatory-mediated tissue damage is triggered and caused by an inherent CNS dysfunction [6].

The prevalence of MS also varies across ethnicity. According to Kurtzke [7], African American males were 40% less likely to develop MS complications than white men, Native Americans, Mexican men, while the prevalence of MS was almost absent among Chinese and Filipino men.

According to studies, women are more prone than men to develop MS. [8, 9]. Nonetheless, because genome-wide investigations have shown no strong evidence for any genes linked with MS located on the X chromosome, the higher prevalence of MS in women might be linked to female-specific physiology, and therefore to hormones.

2.2 Environmental Factors:

Genes have a primary role to play in the likelihood of an individual developing multiple sclerosis. However, environmental factors have a huge impact on the expression of MS. Epstein-Barr virus (EBV), tobacco smoking, and vitamin D deficiency are among the environmental variables that are more strongly linked to MS expression. [5]. Some studies have reported that time of migration and time of exposure to risk factors can influence the expression of MS.

A study carried out by Ascherio [10] showed that nearly all (99%) MS patients had EBV. He went further to report that there is a very low prevalence of MS in adults who have had no history of EBV infection. When comparing those with high anti-EBV antibody titers to those with low titres, those with high titres had a greater chance of getting MS. In pediatric cases, however, the relationship between EBV and MS reduces drastically.

The ingredients in tobacco cigarettes have been linked to a high incidence of MS prevalence [11]. The rate of prevalence was however linked to the dosage of tobacco consumed. Vitamin D appears to be the mediator of the sunshine impact, according to both experimental and epidemiological evidence. High consumption of seafood rich in vitamin D, has been directly correlated to a reduced risk of MS [12], however, this result might be due to the physiological activities of omega-3 fatty acids.

3. CLINICAL MANIFESTATIONS OF MULTIPLE SCLEROSIS

Multiple Sclerosis affects motor movements and causes weakness and fatigue. This is a result of the degeneration of the Corticospinal Tract [13]. MS also results in sensory symptoms which include: numbness, burning pain, and tingling. The clinical manifestations of Multiple Sclerosis include:

3.1 Fatigue:

This is the most common manifestation of MS in patients. The demyelination of axons causes nerve impulse transmission to be delayed and desynchronized to the point that it begins to cease. This results in fatigue experienced by MS patients. Fatigue is expected to worsen in patients who experience MS relapse [14]. The pathophysiology of tiredness may be influenced by changes in the basal ganglia as a result of inflammation [15].

3.2 Cognitive Impairment:

In multiple sclerosis (MS), impairment to the cognitive faculties is a typical occurrence that can develop at any stage of the illness, including the early stages, and can be a major source of disability, social impairment, and poor quality of life [16]. It occurs in about 30% - 70% of a patient with MS [17] which most often involves a decline in complex attention, information processing speed, memory, and executive processes. Language and visuospatial impairments are prevalent in patients with progressive MS.

3.3 Psychiatric Manifestation:

Psychiatric symptoms are typically common in MS patients, and they can aggravate the disease's progression and quality of life. Depression is a common ailment among MS patients, and it's linked to poor medication compliance, lower functional status and quality of life, and an increased risk of suicide. Because of the symptom overlap, diagnosing and treating this disease can be difficult. Depression and anxiety, bipolar illness, psychiatric illnesses, substance misuse, and a variety of other mental comorbidities are all frequent. Personality changes, as well as affect anomalies, might occur as the condition advances [18].

3.4 Neuro-ophthalmologic Manifestation:

The most common neuro-ophthalmologic manifestation of Multiple Sclerosis is Optic Neuritis. It is present in a majority of MS patients. Internuclear ophthalmoplegia, nystagmus, saccadic dysmetria, Pulfrich phenomena, and others are some of the additional symptoms. [19]

4. DIAGNOSTIC EXAMINATIONS OF MULTIPLE SCLEROSIS

Comment [h3]: One table could be introduced regarding latest diagnostic criteria

Multiple sclerosis (MS) diagnostic criteria have been rapidly developing as early as the 1950s, in line with the development of novel and thorough laboratory techniques. The purpose of every single defined criterion up to this point has been to assess the geographic and temporal spread of the clinical presentation caused by lesions in the central nervous system (CNS), as also to rule out other disorders that may resemble MS.

There are no precise indicators for the diagnosis of MS. The medical history and neurological examination are the most important factors in determining the diagnosis. As a result, it is critical to accurately characterize the assaults. In the absence of fever or illness, assaults are characterized as new neurological impairments lasting longer than 24 hours and linked with an

anatomical location. The neurological impairment generally develops subacutely over 2–4 weeks and recovers entirely or partly over 6–8 weeks, either naturally or with corticosteroid therapy [20]

A crucial examination for MS is the lumbar puncture for Cerebrospinal Fluid (CSF) examination. The CSF biochemistry is also examined. The most efficient way to distinguish between infectious and non-infectious CNS inflammatory illnesses is to examine the CSF. CSF pathological alterations can be highly helpful in the diagnosis of individuals with unusual MRI results. Aside from that, electrophysiological testing; Visual Evoked Potentials (VEP), and Somatosensory Evoked Potentials (SEP) can be performed when necessary [21].

Comment [h4]: Brief description of common CSF findings need to be given.

Comment [h5]: Role of imaging particularly MRI needs to be mentioned

5. MANAGEMENT OF MULTIPLE SCLEROSIS

Various therapies for the management of MS have come to light in recent times. However, due to the variability of symptoms expressed, patient accuracy in defining symptoms, clinicians' judgment, there is no fixed management therapy for MS. Management should involve a holistic and patient-specific approach which involves taking into account the family history, symptom expression, subtype of MS being expressed, and laboratory tests. Time management and cost of treatment have limited access to the best possible care across the board for patients. Currently, there is no clear-cut remedy for the treatment of MS. Nonetheless, management therapies have proved to be invaluable in the alleviation of symptoms in patients. Some of the management therapies include:

5.1 Physical Therapy:

Rehabilitation has been proven to improve motor movements. Rehabilitation has a major aim and that is to alleviate the symptoms and drawbacks at the level of physical activity and engagement, using therapies that include personal and environmental factors, to obtain the highest possible independence and quality of life for people with MS within the disease's limitations [22].

The process of rehabilitating patients diagnosed with MS includes evaluation, which is identifying and measuring the consequences of disability. Treatments halt the pathophysiologic mechanisms that lead to tissue damage. Therapeutic exercise focuses on improving organ function. Task reacquisition focuses on total-body adaptive methods. Environmental modification—intensifies efforts to modify the environment (physically, psychologically, socially, and politically) to increase participation [23].

The success of rehabilitation is determined by the severity of the disability and may be impacted negatively by a variety of patient variables (disease duration, cognitive impairments, cerebellar dysfunction, sphincteric symptoms) [24] as well as clinician variables {lack of expertise and time).

5.2 Drug Modulated Therapy:

The most common therapy for MS is corticosteroids. Various studies have looked into the effects of corticosteroids on MS since they were first used in MS in 1951. As a result, there is still a lot of variation in the amount, duration, and type of corticosteroid treatments used to treat MS relapses. These steroids can be administered orally or intravenously with no significant difference in their outcome [25]. Oral administration is less expensive and more convenient. However, it must be stated that treatment with corticosteroids comes with side effects such as insomnia, elevated blood pressure, anxiety, and dysgeusia [26].
Adrenocorticotropic Hormone (ACTH) has also been used in the pharmacological treatment of MS. It's unclear if ACTH's effects on MS relapses reach beyond corticosteroid induction via its

melanocortin receptor-mediated actions, or whether ACTH might help those who have had a poor corticosteroid response recover more quickly. [26]. Further Clinical trials are currently underway.

Elezanumab, Monoclonal antibodies that recognize repugnant guidance molecules A, opicinumab block proteins which are known to act as an inhibition to axonal growth and myelination. They target the leucine-rich repeat and immunoglobulin domain-containing Nogo receptor-interacting protein 1 (LINGO-1), recombinant human immunoglobulin M22, whose target antigen is unknown, and VX15/2503, an anti-semaphorin 4D antibody.[27]

Milder relapses can occasionally be watched rather than treated because most MS relapses are followed by some amount of spontaneous recovery. A patient and a physician should decide whether one should treat or monitor a relapse together, taking into account the impact of both the relapse and the proposed therapy on the patient. Patients who were taught the importance of corticosteroids in relapse treatment treated fewer relapses, preferring oral to IV steroids.

6. CONCLUSION

Multiple Sclerosis is an inflammatory disorder that persists in the Central Nervous System and leads to demyelination, axonal and neuronal injury. While the exact and definite cause has not been traced, the most common risk factors include EBV and Genetic Factors. Symptoms associated with MS are diverse and can vary from one patient to another. The symptoms are also very similar to many other neurologic diseases so it's important for patients to clearly understand and describe their symptoms to the clinicians. The diversity of symptoms also means that the management of MS patients will involve a holistic approach that is narrowed down to meet each patient's specific need.

REFERENCES

[1] Oh J, Vidal-Jordana A, Montalban X. Multiple sclerosis: clinical aspects. Current Opinion in Neurology. 2018;31(6):752–759. https://doi.org/10.1097/wco.0000000000000622

[2] Nourbakhsh B, Waubant E. Neurodegeneration and remyelination in multiple sclerosis. Multiple Sclerosis. 2016:311–337. https://doi.org/10.1016/b978-0-12-800763-1.00013-0

[3] Ascherio A. Environmental factors in multiple sclerosis. Expert Review of Neurotherapeutics. 2013;13(Suppl 2):3–9. https://doi.org/10.1586/14737175.2013.865866

[4] Miller D, Barkhof F, Montalban X, Thompson A, Filippi M. Clinically isolated syndromes suggestive of multiple sclerosis, part I: natural history, pathogenesis, diagnosis, and prognosis. The Lancet Neurology. 2005;4(5):281–288. https://doi.org/10.1016/s1474-4422(05)70071-5

[5] Ramagopalan SV, Dobson R, Meier UC, & Giovannoni G. Multiple sclerosis: risk factors, prodromes, and potential causal pathways. The Lancet Neurology. 2010;9(7):727–739. https://doi.org/10.1016/s1474-4422(10)70094-6

[6] Tsunoda I, Fujinami RS. Inside-Out versus Outside-In models for virus-induced demyelination: axonal damage triggering demyelination. Springer Seminars in Immunopathology. 2002;24(2):105–125. https://doi.org/10.1007/s00281-002-0105-z

[7] Kurtzke JF, Beebe GW, Norman JE. Epidemiology of multiple sclerosis in U.S. veterans: 1. Race, sex, and geographic distribution. Neurology. 1979;29(9 part 1):1228. https://doi.org/10.1212/wnl.29.9_part_1.1228

[8] Orton SM, Herrera BM, Yee IM, Valdar W, Ramagopalan SV, Sadovnick AD et al. Sex ratio of multiple sclerosis in Canada: a longitudinal study. The Lancet Neurology. 2006;5(11):932–936. https://doi.org/10.1016/s1474-4422 (06)70581-6

[9] Hirst C, Ingram G, Pickersgill T, Swingler R, Compston DAS, Robertson NP. Increasing prevalence and incidence of multiple sclerosis in South East Wales. Journal of Neurology, Neurosurgery & Psychiatry. 2008;80(4):386–391. https://doi.org/10.1136/jnnp.2008.144667

[10] Ascherio A, Munger KL. Environmental risk factors for multiple sclerosis. Part I: The role of infection. Annals of Neurology. 2007;61(4):288–299. https://doi.org/10.1002/ana.21117

[11] Hedstrom AK, Baarnhielm M, Olsson T, Alfredsson L. Tobacco smoking, but not Swedish snuff use, increases the risk of multiple sclerosis. Neurology. 2009;73(9):696–701. https://doi.org/10.1212/wnl.0b013e3181b59c40

[12] Kampman MT, Brustad M. Vitamin D: A Candidate for the Environmental Effect in Multiple Sclerosis – Observations from Norway. Neuroepidemiology. 2008;30(3):140–146. https://doi.org/10.1159/000122330

[13] Javalkar V, McGee J, Minagar A. Clinical Manifestations of Multiple Sclerosis. Multiple Sclerosis. Massachusetts: Academic Press; 2016

[14] Braley TJ, Chervin RD. Fatigue in Multiple Sclerosis: Mechanisms, Evaluation, and Treatment. Sleep. 2010; 33(8):1061–1067. https://doi.org/10.1093/sleep/33.8.1061

[15] Finke C, Schlichting J, Papazoglou S, Scheel M, Freing A, Soemmer C. et al. Altered basal ganglia functional connectivity in multiple sclerosis patients with fatigue. Multiple Sclerosis Journal. 2014; 21(7):925–934. https://doi.org/10.1177/1352458514555784

[16] Koutsouraki E, Koutsouraki E. Cognitive Decline and Treatment Strategies in Multiple Sclerosis Patients. Neurology and Neurobiology. 2020;1–7. https://doi.org/10.31487/j.nnb.2020.03.04

[17] Kujala P, Portin R, Ruutiainen J. Memory deficits and early cognitive deterioration in MS. Acta Neurologica Scandinavica. 2009;93(5):329–335. https://doi.org/10.1111/j.1600-0404.1996.tb00005.x

[18] Silveira C, Guedes R, Maia D, Curral R, Coelho R. Neuropsychiatric Symptoms of Multiple Sclerosis: State of the Art. Psychiatry Investigation. 2019;16(12):877–888. https://doi.org/10.30773/pi.2019.0106

[19] Torres-Torres R, Sanchez-Dalmau BF. Treatment of Acute Optic Neuritis and Vision Complaints in Multiple Sclerosis. Current Treatment Options in Neurology. 2014;17(1) https://doi.org/10.1007/s11940-014-0328-z

[20] Lucchinetti C, Brock W, Parisi J, Scheithauer B, Rodriguez M, Lassmann H. Heterogeneity of multiple sclerosis lesions: Implications for the pathogenesis of demyelination. Annals of Neurology. 2000;47(6):707–717. https://doi.org/10.1002/1531-8249(200006)47:6

[21] Ömerhoca S, Akkaş SY, İçen NK. Multiple Sclerosis: Diagnosis and Differential Diagnosis. Noro Psikiyatr Ars. 2018;55(Suppl 1):S1-S9. doi: 10.29399/npa.23418.

[22] Kesselring J, Beer S. Symptomatic therapy and neurorehabilitation in multiple sclerosis. The Lancet Neurology. 2005;4(10):643–652. https://doi.org/10.1016/s1474-4422(05)70193-9

[23] Steins SA, O'Brien B, Young M. The person, disablement and the process of rehabilitation. In: Steins SA, O'Brien B, Young M. 3rd Ed. Physical Medicine & Rehabilitation Secrets. Hanley & Belfus, Mosby: Philidelphia; 1997: pp 1–8

[24] Langdon D, Thompson A. Multiple sclerosis: a preliminary study of selected variables affecting rehabilitation outcome. Multiple Sclerosis. 1999;5(2):94–100. https://doi.org/10.1191/135245899678847220

[25] Burton, J. M., O'Connor, P. W., Hohol, M., & Beyene, J. Oral versus Intravenous Steroids for Treatment of Relapses in Multiple Sclerosis. *Cochrane Database of Systematic Reviews*. 2008. https://doi.org/10.1002/14651858.cd006921

[26] Repovic P. Management of Multiple Sclerosis Relapses. Continuum: Lifelong Learning in Neurology. 2019;25(3): 655–669. https://doi.org/10.1212/con.0000000000000739

[27] Cree B, Ziemann A, Pfleeger K, Schwefel B, Wundes A . Freedman M. Elezanumab in patients with different disease courses of multiple sclerosis: study design and baseline analysis from two phase 2 studies. Multiple Sclerosis Journa. 2020;26(3):219-220.