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Article Review: Multiple Sclerosis

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ABSTRACT

Neurology still puzzles about multiple sclerosis (MS). This comprehensive overview explores MS's history, epidemiology, etiology, clinical manifestations, diagnostic tools, and treatment options. From historical awareness to cutting-edge research, we traverse MS's complex world with a focus on the past and future. Genetics, environment, and migration interact to create geographic riddles in MS prevalence. MS's sensory and cognitive symptoms show its significant influence. Advanced imaging technology and diagnostic criteria enable accurate and quick identification. While transformational, disease-modifying treatments require a tailored approach. Advances have left crucial gaps, prompting researchers, physicians, and policymakers to continue. This in-depth investigation of MS combines historical and future perspectives to emphasize the urgency and possibility of solving this complicated neurological puzzle.

Keywords- Multiple sclerosis, Immunology, Disease modifying therapies.

I. INTRODUCTION

Multiple sclerosis (MS) poses a significant and complex issue in the field of neurology, garnering much interest from researchers, doctors, and those affected by the disease (1). It is a multifaceted and incapacitating autoimmune disorder which affect the central nervous system. It is distinguished by the immune system's erroneous targeting of myelin, the protective covering enveloping nerve fibers (2). The continuous onslaught of this attack results in a series of neurological manifestations, encompassing muscular debility, diminished coordination, sensory disruptions, and cognitive decline (3).

Multiple sclerosis (MS) is a global health concern, impacting a significant number of individuals globally, with its prevalence varying across different geographic regions (4).In addition to its clinical complexities, multiple sclerosis (MS) acts as an exemplary model for studying autoimmune illnesses and demyelinating disorders (5).

This thorough review aims to provide an in-depth exploration of multiple sclerosis (MS), encompassing its historical background, epidemiological aspects, etiological factors, clinical presentations, diagnostic approaches, and therapeutic interventions. In addition, we delve into the nascent domains of multiple sclerosis (MS) research and the pivotal inquiries that persistently confront the scientific community. Through a comprehensive analysis of the various intricate components, our objective is to make a valuable contribution to the collective endeavor of acquiring information, which may eventually result in improved strategies for its care.

1.1 Historical Overview of Multiple Sclerosis:

The historical narrative of MS is a captivating fabric interwoven with centuries of observations and advancements. Although the formal recognition of MS did not occur until the modern period, historical records indicate its existence may have been observed in ancient times (6).

Numerous ancient texts originating from diverse civilizations have ambiguous allusions to symptoms that bear resemblance to those associated with Multiple Sclerosis (MS) (7). Nonetheless, it was not until the 19th century that more comprehensive and elaborate accounts

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started to surface (8). The year 1838 witnessed the notable contributions of Jean-Martin Charcot, a renowned French neurologist, who is widely acknowledged for his role in distinguishing MS from several other neurological disorders (9). Additionally, Charcot is credited for delivering the initial comprehensive clinical description of this condition through a systematic approach. The comprehensive clinical observations made by Charcot established the fundamental basis for our comprehension of multiple sclerosis (MS) as a separate neurological condition (10).

The understanding of multiple sclerosis (MS) was enhanced during the early 20th century due to significant progress made in the fields of pathology and neuroanatomy (8). Prominent researchers, such as Alois Alzheimer and James Dawson, conducted investigations into the specific lesions of brain and spinal cord which are associated with MS, thereby establishing a definitive connection between demyelination and the disease (11).

The advent of MRI in the 20th century brought about a significant transformation in MS diagnosis, enabling the identification and tracking of disease activity at an earlier stage (12). The utilization of this imaging modality facilitated the identification of both active and chronic lesions within the central nervous system, hence providing valuable guidance for making informed treatment choices (13). The development of disease-modifying medications in the late 20th and early 21st centuries has significantly altered C landscape of MS management (14).

II. EPIDEMIOLOGY AND PREVALENCE

The occurrence of MS demonstrates significant regional variations, which are frequently linked to the complex interaction of genetic, environmental, and demographic influences (15).

At a global level, multiple sclerosis (MS) exhibits a higher prevalence in North America and Europe, with a specific concentration in countries situated at higher latitudes (16). Notably, Canada, the United States, and various European nations are prominent examples of regions where MS is more widespread. The prevalence rates of multiple sclerosis (MS) in this context might vary between 50 and 150 cases per 100,000 individuals, indicating that MS is a noteworthy public health issue (17).

On the other hand, regions in closer proximity to the equator, such as sub-Saharan Africa and Southeast Asia, tend to have lower prevalence rates (18, 19). Nevertheless, there are select communities that deviate from the norm and exhibit an increased susceptibility to specific conditions. Notably, the Sardinians in Italy and the Inuit in Canada are examples of such exceptions (20, 21). (Figure 1)

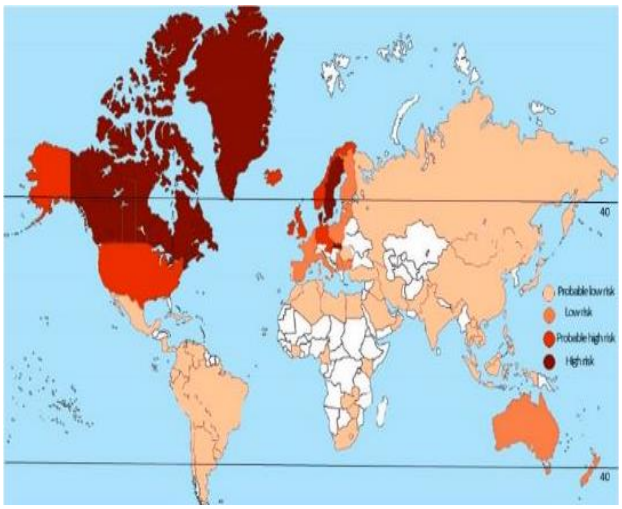

Figure 1: prevalence of MS in different regions in the world (19).

2.1 Risk Factors of MS:

The notion of the "latitude gradient" posits that there is a positive correlation between distance from the equator and multiple sclerosis risk (18). This notion has stimulated inquiries into plausible environmental stimuli, such as vitamin D insufficiency resulting from diminished sunlight exposure in regions situated at higher latitudes (22, 23).

The development of MS is affected by genetics, as confirmed by the elevated susceptibility observed in persons with a familial predisposition to the disease (24). Several genetic markers, including HLA-DRB1*1501, have been found to be correlated with a heightened susceptibility to MS (25, 26).

Environmental factors refer to the external variables and forces that exert an influence on the natural environment, encompassing various physical components such as climate, topography, and natural resources.

Regarding viral infections, some viruses like Epstein-Barr virus (EBV) have been linked to an increased vulnerability for the onset of multiple sclerosis (MS).These infections have the potential to contribute to the deregulation of the immune system (27, 28, 29).

The impact of dietary variables, such as vitamin D intake, omega-3 fatty acids, and antioxidants, on the development of MS has been the subject of research (30). The Western diet, which is distinguished by its elevated levels of saturated fats, has been associated with an augmented vulnerability to MS (31).

Diverse ethnic populations may demonstrate differential vulnerability to multiple sclerosis. For instance, persons of European ancestry exhibit a greater susceptibility in comparison to individuals of African or Asian ancestry (32). Migration studies have demonstrated that individuals who relocate from regions with a lower MS prevalence to places with a greater prevalence may acquire the risk associated with their new location. This implies that environmental influences have a substantial influence (32, 33).

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The prevalence of multiple sclerosis (MS) is higher in women compared to men (34, 35). Also it is often presents throughout early adulthood, typically occurring within the age range of 20 to 40 years. Nevertheless, it has the potential to manifest at any stage of life (36). (Figure 2)

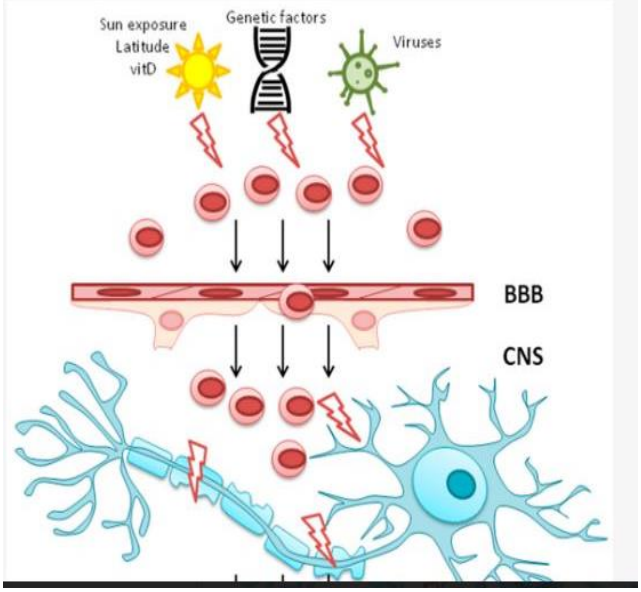

Figure 2: Different risk factors of MS (19).

III. IMMUNOLOGY OF MS

The immunological aspects of MS are centered on the intricate interaction between the immune system and the central nervous system (CNS). MS is categorized as an autoimmune disorder, characterized by the immune system's erroneous recognition of some constituents of CNS, specifically the myelin sheath enveloping nerve fibers. The autoimmune reaction results in the occurrence of inflammation, demyelination (the depletion of myelin), and damage to axons inside the CNS (37, 38).

Autoreactive T cells, including the Th1 and Th17 subsets, have a pivotal role in the immunopathology of multiple sclerosis by instigating an immunological response (39).

The T cells are responsible for the secretion of pro-inflammatory cytokines, hence playing a role in the progression of tissue damage (40). In contemporary times, there has been an increasing scholarly focus on the role of B lymphocytes in the development of multiple sclerosis (41). This interest stems from their capacity to produce autoantibodies and participate in crucial mechanisms such as antigen presentation and cytokine production (42). In multiple sclerosis (MS), the blood-brain barrier (BBB), which serves as a safeguard by separating the circulatory system from the central nervous system (CNS), may experience a loss of integrity. This breakdown permits immune cells to penetrate the CNS, thereby instigating inflammation and demyelination (43, 44).

IV. CLINICAL MANIFESTATIONS AND DISEASE SUBTYPES

MS is distinguished by a diverse array of clinical symptoms and manifestations that exhibit variability among individuals (45). The aforementioned symptoms manifest as a consequence of the immune system's erroneous assault on the CNS, leading to the occurrence of inflammation, demyelination (the degradation of the protective myelin sheath encasing nerve fibers), and impairment of nerve fibers (46, 47) . Clinical manifestation of MS can be classified into numerous distinct domains. Sensory symptoms frequently present themselves as perceptions of numbness, tingling, or paresthesia in different regions of the body, accompanied by either partial or total sensory impairment in specific localized regions (45, 48).

Motor symptoms include muscle weakness, spasticity (characterized by heightened muscle tone and stiffness), as well as impairments in balance and coordination that impact both mobility and fine motor skills (49). Visual symptoms can manifest as optic neuritis, which is characterized by blurred vision, ocular pain, and challenges in perceiving colors (50, 51). Also, double vision may occur due to impairment of the neurons responsible for controlling eye movements (52). Cognitive and emotional symptoms might present themselves in the form of cognitive dysfunction, which impacts memory, attention, and problem-solving skills (53).

Additionally, individuals may experience mood disorders like as despair and anxiety, typically linked to the difficulties given by the illness (54, 55).

The condition of fatigue in individuals with multiple sclerosis (MS) is widely seen and has a significant impact on their daily functioning (56), especially when aggravated by elevated temperatures or physical exertion (57). In addition, persons with multiple sclerosis (MS) may experience speech issues, including dysarthria, which is characterized by slurred speech (58, 59). Furthermore, they may also encounter obstacles related to eating, known as dysphagia (60).

MS spans a range of clinical subgroups, each representing distinct patterns of disease history and development. The subtypes that are most commonly observed in multiple sclerosis (MS) are relapsing-remitting MS (RRMS), secondary progressive MS (SPMS), and primary progressive MS (PPMS) (61).

Relapsing-remitting multiple sclerosis (RRMS) is the most commonly observed subtype of multiple sclerosis, distinguished by its unique clinical characteristics (62). Patients diagnosed with RRMS encounter intermittent episodes characterized by the recurrence or intensification of neurological symptoms. These relapses may manifest as the emergence of new symptoms or the deterioration of pre-existing ones (63).

After experiencing these relapses, individuals then enter phases of partial or total recovery, commonly

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referred to as remissions. The remission periods frequently result in a transient amelioration of symptoms, enabling individuals to restore a certain level of functionality and overall well-being (64). Significantly, in the context of RRMS, relapses exhibit an intermittent pattern, characterized by fluctuations in their intensity, length, and frequency (65). During inter-relapse intervals, individuals commonly endure periods of stability or even exhibit greater amelioration of symptoms, so augmenting their overall quality of life (66).

Secondary progressive multiple sclerosis (SPMS) is a different stage of the disease that frequently occurs after an initial phase of RRMS (67). Within this particular subtype, the ailment undergoes a gradual transformation, transitioning into a progressive trajectory that is distinguished by a consistent escalation in impairment (68).

In comparison to RRMS, which is distinguished by distinct episodes of relapse followed by periods of partial or total recuperation, SPMS involves a transition in the progression of the illness towards a slow accumulation of impairment (67). Although SPMS may exhibit intermittent relapses, these relapses are often less frequent and have a lesser degree of damage compared to those observed in RRMS (69).

Individuals diagnosed with secondary progressive multiple sclerosis (SPMS) may encounter intervals of stability or transient enhancements, sometimes referred to as plateaus (70). However, these occurrences are frequently eclipsed by the overarching pattern of progressive deterioration in terms of impairment (71).

Primary progressive multiple sclerosis (PPMS) is a distinct and comparatively infrequent form of MS that is characterized by a continuous and gradual deterioration of neurological function from the disease's outset (72). PPMS does not exhibit the characteristic pattern of well-defined relapses and remissions (69). Patients diagnosed with primary progressive multiple sclerosis (PPMS) undergo a progressive and consistent deterioration of neurological function throughout the course of the disease (73).

In addition to the aforementioned subtypes, there exist more subtypes that warrant consideration.Progressive-Relapsing Multiple Sclerosis (PRMS) is distinguished by a continuous advancement of the disease from its initial manifestation, accompanied by intermittent relapses occurring on top of the ongoing development. The prevalence of this condition is lower compared to other types of MS (74).

Benign multiple sclerosis (MS) pertains to a certain subset of individuals diagnosed with MS, commonly characterized by relapsing-remitting MS (RRMS), who manifest relatively mild symptoms and demonstrate limited progression of disability over a prolonged duration. (75, 76)

Clinically Isolated Syndrome (CIS) is distinguished by a singular clinical occurrence of neurological symptoms that suggest a possible connection with Multiple Sclerosis (MS), as opposed to being categorized as a separate subtype of the condition (77). Some individuals who have been diagnosed with clinically isolated syndrome (CIS) may experience a progression leading to the development of multiple sclerosis (MS) (78).

V. DIAGNOSTIC METHODS AND CRITERIA

The diagnostic procedure for multiple sclerosis (MS) is a multifaceted undertaking that encompasses a comprehensive assessment of clinical manifestations, an in-depth examination of medical records, and the utilization of diverse diagnostic measures (79, 80). Neurologists depend on a comprehensive neurological evaluation to evaluate the patient's symptoms and medical background, paying attention to the initiation, advancement, and attributes of neurological impairments (81).

The McDonald criteria, specifically the 2017 iteration, hold significant importance within the diagnostic procedure (82). The aforementioned requirements place significant emphasis on the need to effectively demonstrate the temporal and spatial spread of neurological symptoms and lesions through the utilization of imaging studies.

This necessitates the integration of information derived from clinical observations and MRI scans which are utilized for the identification of MS lesions inside the CNS (83). Contrast-enhanced scans are particularly valuable as they effectively emphasize active lesions (84). The investigation of cerebrospinal fluid (CSF), which includes the examination of oligo-clonal bands and the count of cells in the CSF, can offer further indications of inflammation in the central nervous system (CNS) (85).

Evoked potentials, such as visual evoked potentials (VEP) and somatosensory evoked potentials (SSEP), are utilized to evaluate nerve conduction and aid in the detection of demyelination (86, 87).

5.1 Disease Mechanisms and Pathophysiology

MS etiology is multifactorial, making it a complex neurological disease. Extensive study has been conducted to investigate the underlying causes and pathophysiology of this condition. Although the precise etiology of MS still uncertain, numerous theories and research endeavors have provided insights into the pathophysiological mechanisms behind this disease.

One of the prevailing hypotheses posits that the primary characteristic of multiple sclerosis (MS) is primarily attributed to an autoimmune process, in which autoreactive T-cells play a major and significant role. Immune cells infiltrate the central nervous system (CNS) and initiate an inflammatory reaction, leading to demyelination and axonal impairment (88, 89).

Recent research has placed more emphasis on the involvement of B lymphocytes in the pathophysiology

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of multiple sclerosis (MS). These cells are responsible for the generation of antibodies and may potentially contribute to inflammation and demyelination in the central nervous system (CNS) (90, 91). Therapeutic approaches that specifically target B cells have demonstrated promising results in the management of multiple sclerosis (MS) (92).

The heritability of multiple sclerosis (MS) is impacted by genetic factors, particularly specific genetic polymorphisms within the human leukocyte antigen (HLA) genes.These changes have been found to be related with an elevated likelihood of developing MS. Nevertheless, the occurrence of diseases cannot be solely attributed to genetics (25, 93)

Neuroinflammation is a significant characteristic observed in multiple sclerosis (MS), wherein activated microglia and infiltrating macrophages are known to play pivotal roles in the infliction of tissue damage within MS lesions (94, 95). The contribution of immune cell recruitment and CNS inflammation is facilitated by the release of pro-inflammatory cytokines and chemokines (96).

The occurrence of oxidative stress inside the CNS has been identified as a potential catalyst for the impairment of myelin and axonal structures in individuals with MS (97). Recent research findings indicate a plausible association between the gut microbiota and multiple sclerosis (MS), whereby dysbiosis, characterized by disruptions in the composition of gut microbial communities, may exert an influence on immunological responses and the advancement of the illness (98, 99).

VI. CURRENT TREATMENT APPROACHES

The cornerstone of treating multiple sclerosis (MS) is the use of disease-modifying therapies (DMTs), which have three main objectives: controlling inflammation, reducing the rate of relapse, and delaying the course of the illness (100). These treatments come in a variety of forms, such as injectable drugs like Glatiramer Acetate and Interferon Beta, oral drugs like Fingolimod and Dimethyl Fumarate (101), and injection- or infusion-based monoclonal antibodies like Natalizumab, Ocrelizumab, and Alemtuzumab (102).

Furthermore, oral DMT Siponimod has shown promise, particularly in decreasing the course of impairment in secondary progressive MS (103 , 104).

Alongside DMTs, symptomatic treatment is essential for improving the quality of life for people with multiple sclerosis. Corticosteroids are widely used to treat acute symptoms and reduce inflammation during relapses (105). Essential elements of MS care include physical and occupational therapy, which aids patients in regaining their mobility, managing their muscle weakness, and preserving their functional independence (106). Certain MS-related symptoms, such as muscular spasms, discomfort, and bladder dysfunction, are managed using medications intended for symptom treatment, such as muscle relaxants, antispasmodics, and pain relievers (107). To treat severe relapses, disease-specific treatments like plasma exchange may be used in some circumstances (108).

DMTs have been shown to be useful in lowering the risk of relapses and slowing the advancement of the disease; however, individual results may differ and some people may have adverse effects (109). In addition, the expenses and extended dedication linked to the usage of DMT may provide obstacles to accessibility and compliance (110). Interestingly, DMTs are often less successful in MS types that progress, such as primary progressive MS (PPMS), in which inflammation is not as important (111).

By treating a variety of symptoms that are particular to each person with MS, symptomatic management plays a crucial role in improving their quality of life on a daily basis (112). It's important to realize, though, that symptomatic treatments don't change the course of the disease. Rather, they focus on particular symptoms, providing relief and enhancing functionality. Constant therapy and rehabilitation are frequently still essential to the management of multiple sclerosis (MS), enabling patients to effectively control their symptoms and preserve their general quality of life (113).

There are numerous gaps in our grasp of multiple sclerosis (MS), including its mysterious origins, increasing symptoms, biomarkers, neurodegeneration, and environmental factors. MS research and treatment also face significant obstacles. MS problems in academia are caused by several sources. These include the complexity of the disease, the lack of conclusive biomarkers, the difficulties of managing progressive MS, the high cost of therapy, the lack of research funds, and the regulatory hurdles. To solve these difficulties, collaboration, financial allocation, healthcare accessibility, and creative research methods are essential. These elements are crucial to understanding multiple sclerosis (MS) and developing more effective treatments.

VII. DISCUSSION

The era of multiple sclerosis (MS) has significant gains in knowledge and comprehension over the course of history (6). This progress may be attributed to the contributions of influential individuals such as Jean-Martin Charcot (7), as well as the development of neuroanatomy, pathology (8), and diagnostic technology (11, 12). The pursuit of understanding the intricacies of multiple sclerosis (MS) has yielded significant findings regarding the subtle interactions of genetics, environmental factors, and immunological dysregulation (15).

The field of genetics and epigenetics has witnessed notable progress in understanding the influence

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of genes on the susceptibility to multiple sclerosis (MS). Genome-wide association studies (GWAS) have successfully found a multitude of genetic variations that are significantly related with the chance of developing multiple sclerosis (MS) (114). Among these variations, the HLA-DRB1*1501 marker has been extensively studied and its association with MS risk is well-documented (26). The incorporation of epigenetic elements, offers a more comprehensive viewpoint about the interaction between genetic predisposition and environmental impacts. The interplay of dietary factors (31), ethnicity (32), gender, and age within the setting of multiple sclerosis (MS) is intricate and highlights the intricate nature of this condition (34, 35, 36).

An investigation into the worldwide frequency of multiple sclerosis (MS) in conjunction with racial differences reveals noteworthy variations. Regions located at greater distances from the equator are inclined to demonstrate elevated prevalence rates, with significant concentrations observed in North America and Europe (16, 17). Nevertheless, there is evidence to suggest that certain ethnic groupings exhibit varying levels of risk, with individuals of European descent displaying a higher degree of susceptibility (32). The observed disparity implies that there is a distinct interplay between genetic and environmental factors specific to various ethnic groups, underscoring the need for additional comparative studies to elucidate the complexities involved.

The discourse about risk factors associated with Multiple Sclerosis (MS) Nevertheless, the discovery that individuals who migrate to places with high prevalence rates acquire an increased risk suggests the significant impact of environmental factors (33)

The immunological foundations of multiple sclerosis (MS) underscore the autoimmune characteristics of the condition. The role of autoreactive T cells, specifically the Th1 and Th17 subsets, has proven essential in elucidating the underlying mechanisms of multiple sclerosis (MS) pathogenesis (39). Recent studies have shed light on the significance of B lymphocytes, highlighting their possible contribution to the processes of inflammation and demyelination (37, 38, 40, 41). The impaired integrity of the blood-brain barrier facilitates the infiltration of immune cells into the central nervous system, so initiating an inflammatory response and exacerbating tissue damage (43). The complex interaction between chemokines and cytokines plays a crucial role in the regulation of the immune response.

The clinical manifestations of multiple sclerosis (MS) involve a range of symptoms that include sensory, motor, visual, cognitive, and emotional impairments (45, 48, 49, 50, 53, 54). The presence of a wide range of symptoms indicates the varied and diversified characteristics of the disease. The categorization of multiple sclerosis (MS) into several subtypes, such as relapsing-remitting, secondary progressive, and primary progressive, provides a conceptual structure for comprehending the advancement of the disease (61, 62, 63, 67, 69).

The subject of extensive research has been relapsing-remitting multiple sclerosis (MS), which is distinguished by periodic relapses and remissions. This area of study has received significant attention, particularly in relation to the advancement of disease-modifying treatments (64, 65). Secondary progressive multiple sclerosis (MS), characterized by a cumulative accumulation of impairment, highlights the necessity for therapeutic interventions that extend beyond the relapse-remitting stage (68, 70). Primary progressive multiple sclerosis (PPMS), a less prevalent though notably arduous kind, manifests as a persistent and unrelenting deterioration from its first stages, hence demanding a distinct therapeutic strategy (72, 73).

The utilization of sophisticated imaging methodologies, such as diffusion tensor imaging (DTI) and magnetic resonance imaging (MRI), has significantly enhanced our comprehension of the underlying mechanisms of multiple sclerosis (MS) (83). These modalities offer valuable information regarding the microstructural changes occurring inside the central nervous system (CNS) as well as the modifications in functional connectivity (84, 85). The examination of neuroimaging profiles of several subtypes of multiple sclerosis (MS), such as relapsing-remitting, secondary progressive, and primary progressive MS, through comparative research, has the potential to reveal unique patterns of disease development.

Genetic predisposition, environmental aggravators, viral infections, and oxidative stress were all investigated as potential causes of MS. Polymorphisms in the human leukocyte antigen (HLA) genes are known to play a significant influence in MS susceptibility (25, 93). Autoimmunity and autoreactive T cells play a pivotal role in MS pathogenesis (88, 89), with B lymphocytes' growing importance providing subtlety (90, 91). Tissue damage in multiple sclerosis can be understood better via the lens of oxidative stress and its effect on myelin and axonal architecture (97). We gain a broader perspective on environmental contributors by acknowledging the fascinating connection between gut microbiota and MS (98, 99).

Disease-modifying treatments (DMTs) are discussed in depth, with an emphasis on their function in lowering inflammation, preventing relapses, and slowing the development of MS (100).

DMTs cover a wide range of therapeutic modalities, from injectable medicines and oral pharmaceuticals to monoclonal antibodies (101, 102, 104). The significance of symptomatic care in enhancing patients' quality of life in MS is properly emphasized. Multiple sclerosis (MS) symptoms can be treated in a number of ways, including with corticosteroids, physical and occupational therapy, and medication (105, 106).

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VIII. CONCLUSION

In conclusion, multiple sclerosis (MS) remains a major neurology challenge that affects people worldwide. Despite progress in understanding and tackling this difficult topic, the search for better treatments and information continues. Collaboration, funding, innovation, and a commitment to reducing these inequities can improve the future for those with this complex neurological illness. In the search for a cure for multiple sclerosis (MS), scientists are making progress. This development may give people and their families hope and lessen their fight with this painful ailment.

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ISSN: 2583-4053
Volume-3 Issue-1 || February 2024 || PP. 177-186
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