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Multiple Sclerosis: A Review of The Epidemiology, Pathogenesis, Genetics, And Molecular Characteristics

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Abstract

MS is an autoimmune and inflammation-mediated syndrome that causes neurodegeneration and makes the sufferer disabled and incapacitated. The clinical patterns and susceptibility to the disease are different in different populations. Since 1990, The occurrence of MS has risen in various geographic areas, particularly in counties of low and middle income, imposing significant health care and economic burden. Most cases of MS are sporadic but 20% are acquired. Familial Multiple Sclerosis (FMS) is characterized by the presence of at least one affected family member, including those related by first, second, or third-degree connections to the pro-bands. It is estimated to have a global prevalence of approximately 12.6%. The prevalence of MS ranges widely among Arabs and is lower than in Western countries but the rate is expected to increase over time and thus required the attention of the scientific world. The etiological features of the disorder are still unknown and extensive genetic level research is still required to make progress in understanding the causation of the disease. Furthermore, future investigations should include well-designed clinical trials examining the efficacy and safety of licorice-derived drugs in MS patients to bridge the gap between preclinical discoveries and clinical applications. These trials can provide useful insights into the real-world applicability of licorice-based treatments, perhaps influencing their incorporation into routine MS treatment procedures. This study will provide insight for future researchers who are willing to work in the area of medical genetics.

Keywords: Autoimmune Disease, Epidemiology, Genetics, Multiple Sclerosis, Pathogenesis

1. Introduction

Multiple Sclerosis (MS) is a persistent autoimmune inflammatory condition that affects the central nervous system, leading to various neurological impairments. The disease causes abnormalities that disrupt the nerve impulse and results in various neurological disorders. The patients become incapacitated or disabled due to uncontrolled nervous system deterioration. Their mobility is compromised and they require constant care (Alonso & Hernán, 2008). Most of the MS cases are sporadic but 20% are hereditary (Ramagopalan et al., 2011).FMS is characterized as a subtype of MS where individuals with the condition have at least one family member, including those related by first, second, and third-degree connections, as well as relatives of pro-bands, who are also affected by MS (Hader & Yee, 2007).

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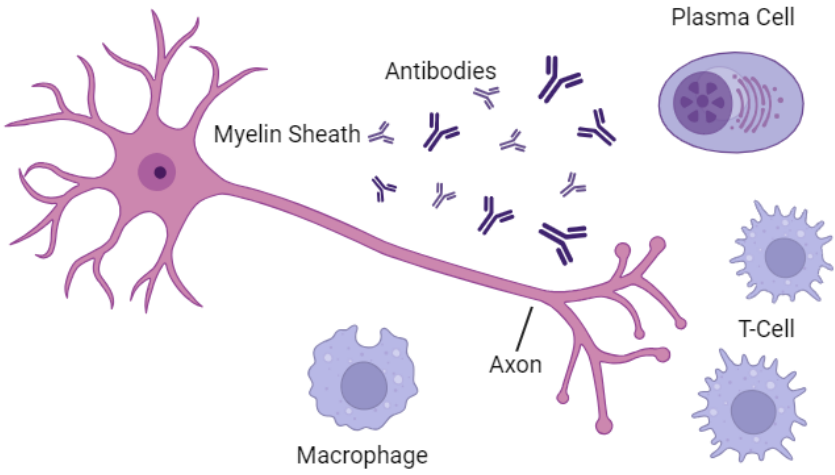

Figure 1 Autoimmune attacks on Myelin

MS is a common inflammatory neurological condition, affecting approximately 33 individuals per 100,000 worldwide. This disease presents distinct clinical patterns and susceptibility factors that vary among different populations. Notably, since 1990, the prevalence of MS has seen a substantial increase, particularly in low and middle-income countries, resulting in considerable healthcare and economic burdens (McGinley, Goldschmidt, & Rae-Grant, 2021). The earliest documented case of FMS dates back to 1933, as reported by Curtius. The prevalence of MS demonstrates significant variations between countries, with higher rates observed in Europe and North America, exceeding 100 cases per 100,000 population, while lower rates are seen in Sub-Saharan Africa and Eastern Asia, with only 2 cases per 100,000 population (Vidal-Jordana & Montalban, 2017). The worldwide FMS prevalence was reported at 12.6% according to a recent meta-analysis and systemic review of FMS occurrence. This study has also shown that there is a great diversity in prevalence among different countries such as 32.7% in Saskatchewan, and 2% in Hungary. Another study investigated that there is a higher FMS risk in males than females in Iran (Vidal-Jordana & Montalban, 2017).

The Arab population is predominantly spread across two major continents, Asia and Africa, comprising a total of 315 million individuals. Additionally, there are approximately 12 million Arabs residing in North America and Europe (Morgan, 2008). Within the same geographic region, other non-Arab ethnic groups such as Kurds, Black Africans, and Berbers also reside (Ahmed 2017). It's important to note that data on MS incidence is available primarily for specific Arab populations, including Jordanian, Saudi, Palestinian, Iraqi, Omani, Libyan, and Kuwaiti populations (Hajjej, Almawi, Arnaiz-Villena, Hattab, & Hmida, 2018).

A review spanning from 1975 to 2007 revealed varying MS incidence rates among different Arab populations. For instance, in the Arab-born population residing in Greater Jerusalem, the incidence of MS was 0.7 cases per 100,000 individuals per year. In contrast, the incidence rate in Kuwait was higher at 2.08 cases per 100,000 population per year (Sinniah et al., 2014).

The prevalence of MS ranges widely among Arabs and is lower than in Western countries. The rate is expected to increase over time. The clinical pattern of MS is comparable to “Western countries” but there are problems with diagnostic testing and optic-spinal disease features.

Furthermore, the data on MS prevalence in Arab immigrants and Arab- Americans in Europe could be helpful to understand the migration effects from lower to higher risk areas (Benamer, Ahmed, Al-Din, & Grosset, 2009).

The precise pathogenesis and etiology of the disease remain elusive, given that it involves intricate interactions between environmental and genetic factors. Numerous studies have pointed to a combination of genetic, infectious, and environmental factors as potential contributors (Ghasemi, Razavi, & Nikzad, 2017). Moreover, the prevalence of MS tends to rise following adolescence, peaking between the ages of 25 to 35. Genetic predisposition is recognized as a significant factor in the development of MS, and it is noteworthy that females are more frequently affected by the condition than males (Loma & Heyman, 2011).

Genetic factors contribute to approximately 30% of the susceptibility to this disease. Over 100 genes and gene loci have been associated with MS . Numerous studies have demonstrated a familial tendency for MS, as well as a high level of concordance among twins and relatives of affected individuals (Thorsby & Lie, 2005). While some genetic variations have been examined among family members of MS patients, the results have not provided definitive evidence regarding the specific genes involved in the disease (Wolters & Wijmenga, 2008). The complex etiology of MS has been recognized by researchers, who also note that a number of genes, including proteolipid protein (PLP), myelin oligodendrocyte glycoprotein (MOG), myelin-associated glycoprotein (MAG), and myelin basic protein (MBP), may be susceptible. These genes are regarded as potential genetic loci for vulnerability to FMS. However, their direct linkage to the disease remains a subject of controversy and requires further investigation to pinpoint the exact genetic contributors (Amos, Driscoll, & Hoffman, 2011).

Beyond genetic factors, MS onset is influenced by various environmental factors. These include factors such as smoking, the Epstein-Barr virus (EBV),

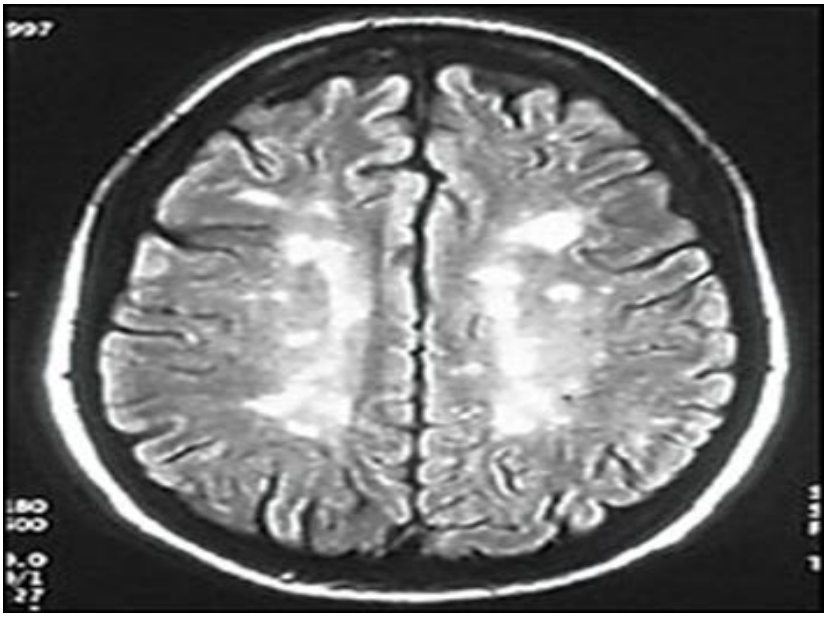

Figure 2 Fluid attenuation inversion recovery (FLAIR) transverse section image of the brain with multiple sclerosis. The lesions are shown in high signal white matter and periventricular region (Double Inversion Recovery Brain Imaging at 3T: Diagnostic Value in the Detection of Multiple Sclerosis Lesions, 2007)

and fluctuations in serum vitamin D levels. Moreover, environmental elements such as obesity and exposure to infectious agents also play a role in MS development (Mechelli et al., 2010). Diagnosing MS relies on the detection of lesions that are both spatially and temporally distributed within the central nervous system. It's important to note that relying solely on a single diagnostic test is not a reliable approach for identifying MS due to the possibility of other medical conditions presenting with similar symptoms (Handel, Giovannoni, Ebers, & Ramagopalan, 2010).

Since there are still limitations and areas to overcome to open new horizons in research toward medical success in the prevention and cure of this disorder. Novel research is needed for the identification of causative variants that contribute to the development of the disease via the latest and defined research methods and optimum research design (Wingerchuk, 2011).

2. Pathogenesis and clinical features

The pathophysiological characteristics of MS can be divided into two phases: (1) inflammatory, and (2) neurodegenerative as shown in Fig. 1 (Steinman 2001). The pathogenesis mechanism and autoimmune attack on the myelin leading to MS is shown in the figure 1 below. The most common clinical symptoms of MS involve loss of balance and coordination, bladder dysfunction, numbness, mood changes, weakness, cognitive dysfunction, pain, fatigue, and vision impairment (P. S. Rommer et al., 2019). The figure 2 below represents the fluid attenuation inversion recovery (FLAIR) transverse section image of the brain with MS.

3. Genetics study of MS:

A Genetics study of MS revealed that it is a polygenic disease like asthma disease and diabetes. which suggests that certain underlying mechanisms beyond DNA assist the onset of disease (P. Rommer & Zettl, 2022). A wide spectrum of factors falls within this category, encompassing environmental elements such as viral infections, smoking habits, and dietary factors, as well as epigenetic factors that include histone modifications, non-coding RNAs, and DNA methylation. Furthermore, the causative factors of MS involve numerous genes and pathways (Kister, Bacon, & Cutter, 2020).

T cells may assault brain cells directly if their T cell receptors are altered or mutated. T lymphocyte activation is a two-step procedure. The contact between an antigen presented by the MHC on the surface of antigen-presenting cells (APCs) and the T cell receptor (TCR) results in the first signal. The second signal is produced when co-stimulatory receptors on T cells are bound by ligands on APCs. T cells undergo apoptosis in the absence of this second signal, essentially blocking the start of an immune response (Hecker, Bühring, Fitzner, Rommer, & Zettl, 2021). Through analysis, it has been observed that the G allele in rs231775A > G of the CTLA-4 gene is linked to a higher susceptibility to MS only in individuals with the HLA-DRB115:01 genotype. It's important to note that studying the CTLA-4 gene alone, without considering HLA-DRB115:01, does not confer susceptibility to MS. Further analysis has shown that heterozygotes with AG have a 1.5 times higher risk of MS than individuals with the AA genotype, while GG individuals have a 2-fold higher risk than those with the AA genotype (Wagner et al., 2015). Signal peptides play a crucial role in transporting the protein to the lymphocyte surface, and even slight alterations in a signal peptide can affect the intracellular transport of the CTLA-4 molecule, influencing its accessibility on the surface of T cells. A missense mutation (Thr>Ala) results in changes to the overall signal peptide structure, directly impacting the inhibition of T cell activation via CTLA-4 (Borysewicz-Sańczyk et al., 2020).

3.1. Familial Occurrence Of MS

It has been observed that consanguinity is prevalent in the Arab population and

FMS is quite common in several countries, however, there is an obvious shortage of beneficial population-based genetic studies in the Arab population. The genetic basis of MS was laid with the identification of familial aggregation in the 1980s (Rodríguez-Sánchez et al., 2023). The contribution of genetics to MS is raised from both familial and twin clustering studies. Both identical and monozygotic twins have been observed to showcase significantly greater clinical concordance rates (25% to 30%) than fraternal or dizygotic twins (3% to 7%), a difference that has a possible impact on the less penetrance of this ailment, that is, the lower chance that a particular genotype would express in MS. 15% TO 20% MS patients has demonstrated familial occurrence of MS that is much more than the prevalence in general population (Eichhorst et al., 2019).

The risk is greatly increased for first-degree relatives of MS patients and is estimated to be 3%. Particularly, siblings have a 4% risk, whereas parents and children have a 2% risk. This risk is 10 to 30 times greater than the age-adjusted risk in the general population, which normally varies from 0.1% to 0.3%, and is three times higher compared to second- and third-degree relatives, who have a 1% risk (Agre et al., 2020). Complete siblings are more vulnerable than half siblings, and the risk increases when both parents have MS. However, adopted people and step-siblings of index cases run the same risk as the general populace. As a result, there is a nonlinear link between the degree of genetic material shared with the sick family member and the probability of FMS recurrence. Monozygotic twins had a recurrence risk of 18.2%, whereas siblings have a risk of 2.7%, resulting in a sibling relative risk (s) of 16.8 according to a thorough meta-analysis of over 500 papers (Hu et al., 2019).

One study from Iran reported that MS is prevalent among sisters whereas the father-son relationship has the lowest association (Salehi, Almasi-Hashiani, Sahraian, & Eskandarieh, 2020). Mohammed et al. found that parental consanguinity is more common in FMS patients and reported evidence that the increasing prevalence of MS in Saudi Arabia could be multifactorial (Evans, Levasseur, Cross, & Piccio, 2019).

According to research, the NLRP1 gene possesses a mutation (Gly587Ser) that may be the cause in the families studied, pointing to an autosomal recessive genetic tendency. These variations demonstrated elevated IL-1B gene expression, active cytokine production, and general immunologic pathway activation linked to NLRP1. This variant comprises altered amino acid residues of NACHT, an evolutionarily highly conserved domain, that was required for the correct NLRP1 inflammasome assembly and oligomerization (Tupik, Nagai-Singer, & Allen, 2020). The pathogenic variant of NLRP1 can be validated by the reported genetic associations and continuous activation of NLRP1 inflammasome that directly lead to the constant overproduction of mediators such as IL-1β as produced in MS and malignant melanoma tissues. IL-1β is involved in different types of inflammatory and neurodegenerative processes that occur during MS, evidence also suggests that IL-1β is involved in the migration of activated T cells across the blood-brain barrier. IL-1β is usually present in CNS lesions and its concentration increases in CSF fluid in MS patients (Muela-Zarzuela et al., 2023).

3.2. Candidate Gene Studies

The initial population studies investigating hereditary factors in MS laid the foundation for identifying genetic contributors. However, the early phase of association studies was hindered by numerous small-scale investigations that lacked the statistical power needed to identify genuine associations. The MS gene database (msgene.org) serves as a comprehensive historical repository containing over 700 genetic studies pertaining to MS. Despite the limited

confirmation of genetic findings in MS studies, only a handful of authentic associations have been established. Notably, the human leukocyte antigen (HLA) gene cluster located on chromosome 6p21 has emerged as the most significant locus in MS research, both through candidate studies and microsatellite markers (Vilariño-Güell et al., 2019).

In a study conducted by Ogawa et al., the association between HLA genes and MS susceptibility was investigated. Their findings confirmed that the most robust association with MS was linked to HLA-DRB115:01. Through a stepwise conditional analysis, they were able to identify HLA-DRB104:05, HLA-B39:01, and HLA-B15:01 as independent factors contributing to MS susceptibility. This reaffirmed prior research that had already established a strong connection between HLA genes and MS, with HLA-DRB1*15:01 having the most substantial impact on susceptibility to the disease. Importantly, both class I and class II HLA genes were found to independently confer susceptibility to MS (Szymczak, Colli, Mamula, Evans-Molina, & Eizirik, 2021). Furthermore, the study identified two specific MS risk factors associated significantly with HLA-DRB1*15:01 and a particular amino acid, phenylalanine 9, at HLA-DQβ1. The exact mechanisms by which these variants are formed or exert their effects remained unclear. Nevertheless, based on their validation efforts, the study suggested that HLA-DQβ1 Phe9 plays a causal role in HLA gene variants contributing to MS (Kaufmann et al., 2022).

3.3. Genome-Wide Association Studies (GWAS)

The first genome-wide association study (GWAS) on people with MS was carried out by the International MS Genetics Consortium (IMCGC), and the results were published in 2007. In addition to a replication cohort made up of 2,322 MS patients and 2,987 healthy people, this study included 931 family trios (Wen & Yu, 2023). In the original GWAS, a variable known as rs12722489, located in the first intron of IL2RA, was identified as a significant genetic connection in MS that was not associated with the major histocompatibility complex (MHC). The interleukin-2 receptor, which plays crucial roles in several immunological pathways, is encoded by the IL2RA gene. More recently, the largest genetic study on MS to date, which included 47,351 patients and 68,284 controls, identified 233 genome-wide loci that increase the chance of getting MS (Afrasiabi et al., 2019).

MS has been linked to 17 genetic variations discovered through whole-exome sequencing, according to genome-wide association studies. Of these 17 variations, they found one in the TRIOBP gene that was significantly different from the average person without MS and multiple sclerosis. The amino acid Ala>Ser was substituted as a result of this missense variation (Chr22: 37723520G>T, Ala322Ser, rs201693690), which was present in exon 7 (Ahangari et al., 2022). Another research, which was reported in ExAC, discovered a connection between it and schizophrenia and deafness. which was described in ExAC, identified a link between it and deafness and schizophrenia. Compared to the ExAC research, the allelic frequency of this variation in MS patients was much higher (19% vs. 0.05%). The development of the risk of MS may be linked to the existence of this variation. Despite the fact that the TRIOBP gene is associated with the control of cell migration and proliferation, aberrant protein aggravation can result in persistent mental disease (Shepard, Cline, Hinds, Jahanbakhsh, & Prokop, 2019).

3.4. Rare Variants

The attainment of GWAS in the discovery of common variations has opened doors for the detection of rare variants. Exome sequencing has been used to investigate MS cases from 43 families that had four or more index cases and identified a rare pathogenic variant in the CYP27B1 gene that led to total loss of

gene function in one of the participants. However, extensive replication and specific sequencing research failed to reproduce the results (Goris, Vandebergh, McCauley, Saarela, & Cotsapas, 2022). One more research discovered that a mutation p.Arg415Gln in NR1H3 leads to an extreme and progressive mendelian form of MS. No confirmation was possible in research of 36,538 controls and 32,852 cases. Furthermore, one research that used the Exome Aggregation Consortium (ExAC) discovered numerous individuals with p.Arg415Gln in NR1H3 but no testified MS or relevant disorder. A handful of studies have been reported that identified rare pathogenic variants in the Arab region through exome sequencing (Hočevar, Ristić, & Peterlin, 2019). One paper performed a replication analysis of non-HLA rare MS pathogenic risk variants in the Kuwaiti population of 170 cases and 311 controls. The researchers studied the association of a set of risk variants of MS and authenticated the outcomes in replication research of a uniform Kuwaiti background. Till 2018, no evidence has been found related to the monogenic MS, and at-length investigation via exome sequencing methods needs to be used. Any associations in MS for rare pathogenic variants are still to be proven (Villarreal et al., 2021).

4. Environmental factors

4.1. Relation to Infections

Different infections have been implicated in the pathogenesis of MS, usually in constant association with past infections of Epstein-Barr virus (EBV) (Ahmed, Aziz, et al. 2019). The relationship between EBV and MS has been studied in Kuwait and both have mentioned conflicted results. One report has shown no relation between EBV and MS, and the other one exhibited a substantial association (Baker, Amor, Kang, Schmierer, & Giovannoni, 2020).

Measles, a member of paramyxovirus, is quite contagious. The transmission of the virus occurs via direct contact or through airborne droplets and affects the air tract, with consequent extends to the entire body. Three studies have been conducted, two of them were carried out in Saudia, and one in Kuwait. The studies from Saudia showed that measles make individuals more susceptible to MS. In contrast, the report from Kuwait showed no association between measles and MS (Maroufi, Mortazavi, Sahraian, & Eskandarieh, 2021).

For human herpesvirus-6 (HHV-6), one report conducted in Kuwait showed no relevance to MS risk (Maroufi et al., 2021). The same is the case for mumps reported in a study from Kuwait. For varicella-zoster virus (VZV), three studies were conducted, one in Kuwait and two in Saudia, and all three of them have reported no association with MS risk (Alluqmani, 2023).

4.2. Role of Vitamin D

The concept of vitamin D as an explanation for the latitude gradient was first proposed by Goldberg in 1974. In humans, the primary source of vitamin D is exposure to ultraviolet B (UVB) radiation from sunlight (Gombash, Lee, Sawdai, & Lovett-Racke, 2022). It has been studied in a retrospective observational report of about 10,709 individuals in Saudi clinics and hospitals, that 83.6% of the cases were deficient in vitamin D (Gombash et al., 2022), which is quite high considering its contribution towards MS risk (Gombash et al., 2022).

Correction of vitamin D levels might influence the cognitive activities in MS cases, apart from its function in bone health and immune defenses. Recent research has revealed that while vitamin D plays a role in the latitude effect associated with sunlight exposure, it is not the sole mediator, but rather an associated risk factor for MS . Vitamin D's immunomodulatory effects on the immune system have implications for its impact on MS risk, as do the persistence and severity of Epstein-Barr virus (EBV) infection (Galoppin et al., 2022).

One study has reported an inverse relationship between EBV DNA load and

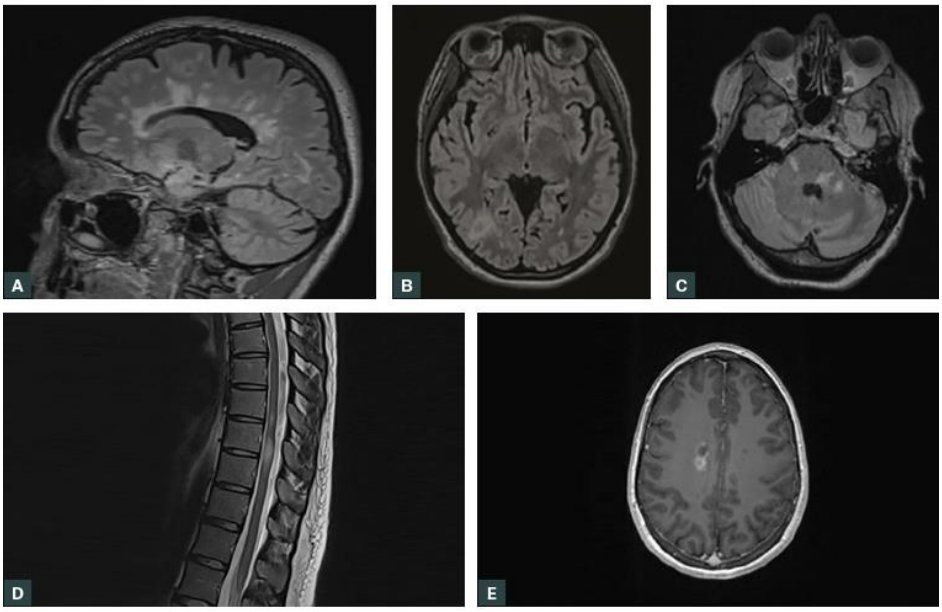

Figure 3 A Typical multiple sclerosis magnetic resonance imaging finding from several patients (Travers et al., 2022)

serum 25(OH)D levels in individuals without MS. However, this study did not provide significant evidence to support an increased risk of MS due to interactions between vitamin D deficiency and EBV infection. It suggests that while both vitamin D and EBV infection may be relevant factors in MS, their combined effects in increasing MS risk are not well-established (Brütting, Stangl, & Staege, 2021).

4.3. Smoking

In a study of a North American cohort, more than 50% of MS patients were smokers and the patients are heavier smokers than the general population of smokers, and they keep on smoking even after diagnosis of the disease. It is also common in people of the Middle East and North Africa, particularly in males, having a prevalence of about 50% in several countries of MENA (Hanaei, Sahraian, Mohammadifar, Ramagopalan, & Ghajarzadeh, 2021).

Sundstrom et al. examined plasma cotinine levels as a measure of tobacco exposure and found an increased risk in females with passive cigarette smoke exposure. One meta-analysis observed the impact of smoking on dose response on MS risk, but the authentication methods did not appear to be reliable. It has been studied that pregnant smokers do not increase the risk for the progression of MS in the exposed unborn child, however, in another case it turned out to make the child more susceptible to MS (Miclea, Bagnoud, Chan, & Hoepner, 2020).

4.4. Dietary Intake and Supplements

Both in vitro (conducted in controlled laboratory environments) and in vivo (conducted in living organisms) studies have indicated that lower sodium intake and reduced intracellular sodium concentrations can have a protective effect on the immune system. However, the findings of a recent case-control study suggest that there is no significant association between dietary sodium intake and the risk of developing MS . These results imply that the relationship between dietary sodium and MS risk may not be straightforward and require further investigation (El-Salem et al., 2021).

4.5. Impact of Pollution

The relationship between air pollution and MS is still not fully understood. However, there is evidence suggesting a potential connection. Exposure to particulate matter in the air can initiate an inflammatory response in the lungs, leading to increased levels of systemic inflammation and inflammatory cytokines. Prolonged exposure to air pollution has also been linked to damage to the blood-brain barrier and neuro-inflammation (Abbaszadeh et al., 2021).

Several studies have indicated a significant association between MS and exposure to specific air pollutants, including carbon monoxide, lead, and sulfur dioxide. These findings suggest that air quality and pollution levels may play a role in the development or exacerbation of MS, although further research is needed to fully elucidate the mechanisms and extent of this association (Bergamaschi et al., 2022).

5. Diagnosis

Diagnosing MS relies on the presence of lesions that are disseminated both in space and time within the central nervous system. Relying solely on a single diagnostic test is not considered reliable for identifying MS, as various other medical conditions can present with symptoms similar to those of MS, making it necessary to consider multiple clinical and diagnostic criteria for an accurate diagnosis (McGinley et al., 2021). Magnetic resonance imaging is a highly sensitive detection method for silent MS plaques. The clinical findings of imaging are included in the diagnostic criteria proposed by investigators. It explains the characteristics of MS lesions, such as location (infratentorial, spinal, juxtacortica), number (nine or more), and lesion enhancement using a contrast medium (Solomon et al., 2023).

A brain MRI is considered a confirmatory diagnostic tool for MS (Figure 2). It helps identify lesions in areas with high signal intensity, such as the spinal cord or cerebral white matter. MRI provides detailed structural information about these lesions in regions including the cervical cord, craniocervical junction, and posterior fossa. It plays a crucial role in visualizing the pathological changes associated with MS and is a valuable tool for diagnosing the condition (Yamout et al., 2020).

Other confirmatory tests include cerebrospinal fluid analysis in which higher IgG concentration is found in MS patients. Other blood tests involve the determination of thyroid hormone level, vitamin B12, erythrocyte sedimentation rate anti-neutrophil antibodies, and T-lymphocytes, but these tests are not specific as they can mimic other disease conditions (Jakimovski, Awan, Eckert, Farooq, & Weinstock-Guttman, 2022).

A. periventricular lesions (FLAIR sequence); B. right parieto-occipital juxtacortical lesion (FLAIR sequence); C. Lesions in the brainstem and cerebellum (FLAIR sequence); D. Spinal cord lesions in the thoracic cord (T2-weighted turbo spin echo sequence); E. Gadolinium-enhancing lesion (T1-weighted sequence).

6. Treatment

Treatments of MS include agents for immune suppression and immune modulation since the 1980s. These conventional treatments usually do not inhibit inflammation in the central nervous system (Hauser & Cree, 2020).

6.1. Symptom Specific Treatments

Symptom-specific treatment is significant to enhance life quality in younger and older MS patients. For example, a neurogenic bowl is treated with dietary fiber intake, adequate hydration, and bulk-foaming agents. Neuropathic pain is treated with specific serotonin uptake inhibitors, anticonvulsants, and tricyclic antidepressants (Brownlee, Bourdette, Broadley, Killestein, & Ciccarelli, 2020). Hydrotherapy also has the potential for pain management. Muscle spasticity is treated by Baclofen, which is a first-line agent and helps to decrease alpha motor neuron activity (Chisari et al., 2021).

6.2. Disease-Modifying Agents

Disease-modifying agents are used to sustain and preserve a healthy immune system by suppressing the T-cells cascade responsible for axonal damage and demyelination. The Food and Drug Administration (FDA) has approved seven agents for the treatment of MS . These include teriflunomide, dimethyl fumarate, glatiramer acetate, natalizumab, fingolimod, mitoxantrone, and interferon beta (Otero-Romero, Ascherio, & Lebrun-Frénay, 2021). These diseases modifying therapies are effective only if they are started in an earlier stage of disease progression. The limitation of disease modification include reactions at the injection site, inflammation, edema, leukopenia, suicidal thoughts, neutralizing antibodies, elevated liver enzymes, and influenza-like symptoms (Rostami Mansoor & Ghasemi-Kasman, 2021).

The application of new potent agents having a high potential to inhibit inflammation within the central nervous system is introduced. These new drug agents are associated with adverse effects even death. Therefore, no effective treatments for the disease progression stage are available (Amato et al., 2020).

7. Conclusion

In conclusion, MS MS remains a complex and multifaceted disorder with significant variations in clinical patterns and susceptibility among different populations. The rising prevalence of MS, particularly in low and middle-income countries, underscores the urgent need for increased attention and research efforts to address the growing health care and economic burdens it imposes. The familial component of MS, represented by FMS, reveals the involvement of genetic factors in disease predisposition, with a global prevalence of approximately 12.6%. Despite extensive research, the exact etiological factors underlying MS remain elusive, emphasizing the ongoing necessity for rigorous genetic investigations to unravel the disease's causative mechanisms. Notably, the prevalence of MS within Arab populations, while currently lower than that in Western countries, is anticipated to rise, necessitating heightened scientific focus and collaboration to understand and manage this emerging challenge. Comprehensive genetic studies, including whole exome sequencing followed by confirmatory Sanger sequencing, hold promise in identifying rare pathogenic variants that contribute to the disease's development. These advancements not only shed light on the underlying molecular pathways driving MS but also pave the way for the discovery of novel biomarkers and potential therapeutic targets.

In the quest to decipher the intricate interplay between genetics, environment, and disease manifestation, ongoing efforts are crucial for enhancing our understanding of MS. The insights gained from unraveling the genetic underpinnings of MS through meticulous research will undoubtedly contribute to more accurate disease prediction, improved diagnostic methods, and the development of innovative treatments. As we continue to delve into the intricacies of MS, the scientific community's collaborative endeavors hold the promise of improving the lives of those affected by this challenging disorder.

8. Declaration Statements

Protection of Privacy: Not Applicable

Ethics Approval: Not Applicable, as no humans or animals were utilized in this study.

Conflict of Interest: There is no conflict of interest among the authors, all the authors have contributed equally in this work.

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Authorship Contribution Statement: A.A designed, proposed and supervised this study, B.A performed the literature review

and I.A proofread and revised the manuscript.

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