Review Article

Factors Involved in Relapse of Multiple Sclerosis

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Abstract

Multiple sclerosis (MS), a chronic autoimmune disorder, affects the central nervous system (CNS). It affects the brain, spinal cord, and optic nerve, leading to problems with vision, balance, muscle control, and other basic bodily functions. MS relapse (MSR) involves an acute inflammatory demyelinating reaction within the CNS. This review focuses on the main factors involved in MSR based on a detailed literature search. Evidence suggests that MSR is influenced by age, sex, pregnancy, serum levels of Vitamin D, interactions between genetic and environmental factors, and infectious diseases. Many of these factors are modifiable and require the attention of patients and health-care providers if favorable outcomes are to be realized. Identification of MSR risk factors can help in the development of therapies that could be used to manage MS and MSR.

Keywords: Demyelinating, immune system, multiple sclerosis, relapsing–remitting

Introduction

Multiple sclerosis (MS), a chronic autoimmune disorder of the central nervous system (CNS), was first described in 1868 by Jean-Martin Charcot. The term refers to the numerous scars (sclerae; better known as "plaques" or "lesions") that develop in the white matter of the brain and spinal cord. In 2015, approximately 2.3 million people were affected worldwide, with prevalence varying widely in different regions and among populations. Moreover, approximately 18,900 people have died from MS, increased from 12,000 in 1990.[1] MS usually presents between the age of 20 and 50 years and is twice more common in women than men.

MS takes two forms, with new symptoms either occurring in isolated attacks ("relapsing") or building up over time ("progressive").[2] Between attacks, symptoms may disappear completely, but permanent neurological problems often remain, especially as the disease advances. Disease progression is characterized by plaque formation in the white matter, axonal injury, and demyelination, mainly in the spinal cord, optic nerve, brainstem, and periventricular regions. Chronic diseases such as MS can also cause immense emotional stress, which can lead to secondary symptoms such as fatigue, confusion, and depression. Depression can also be a side effect of some MS drugs, such as corticosteroids and interferon. Stress-relieving activities, such as meditation and yoga, have been shown to help people suffering from MS.

There is no cure for MS. Current treatments attempt to improve function following an attack and prevent new attacks.[3] The medications used to treat MS, although modestly effective, can have adverse side effects and be poorly tolerated;[4] physical therapy can also help improve function.

Approximately 80% of patients experience an initial clinical episode of demyelination, in a condition known as "clinically isolated syndrome" (CIS),[5] which involves infiltration of inflammatory cells. Approximately 85%–90% of MS patients characterized by initial CIS attacks present with relapsing–remitting disease: acute inflammatory demyelinating reactions, also referred to as "flares" or "exacerbations," followed by partial or complete recovery. Relapses tend to last for ≥24 h, without accompanying infection or fever.[6] MS relapse (MSR) leads to visual impairments in 21.5% of patients and paresthesia in 54.3%.[7] Other symptoms can include extreme weakness, as well as dysfunction of the bowel, cerebellum, and bladder, depending on the involvement of

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pyramidal tracts. MSR linked to pyramidal damage, sphincter dysfunction, or the cerebellum is more severe and requires prompt treatment.[1]

The most important tool for MSR assessment is physical examination (blood pressure, heart rate, and temperature), followed by neurological examination (strength, vision, coordination, gait, and sensation). Vision testing involves examination of eye movements, visual acuity, visual fields, and color vision. These tests are important because there is an increased risk of developing optic neuritis among patients with MSR. Evidence of brainstem involvement is likely to be revealed through neurological examination, based on symptoms including speech changes, altered facial sensation, and double vision.[8] Transverse myelitis can be revealed on the basis of abnormalities in strength and sensation. Problems in coordination, gait, and tremor are associated with altered functioning of the cerebellum. The results of neurological examinations conducted previously should be compared with the current results to guide the diagnosis of new relapse or symptom progression.

Magnetic resonance imaging (MRI) is used to assess MS activity and disease progression. Different sequences of MRI can reveal important features of the disease. For instance, T2 fluid-attenuated inversion recovery sequence can be used to measure the total disease burden on the basis of the accumulated number and size of lesions.[8] However, newly developed lesions are not apparent immediately upon imaging; therefore, MSR assessment should not be based exclusively on MRI.

The exact etiology of MS remains unclear, but a combination of infectious agents and environmental and genetic factors has been postulated to be involved in disease pathogenesis. In this review, we summarize the current research focusing on these and other factors and some of the agents used to manage MS.

Main Factors Involved in Multiple Sclerosis Relapse

Relapses are the main challenges faced by health-care providers with regard to the treatment and management of MS.[6,9] Although relapses are an essential element in the diagnosis, treatment, and prognosis of MS, they also lead to increased health-care costs.[9,10] Thus, attempts have been made to identify and mitigate factors that can increase the risk of relapse among MS patients.[6,10]

MSR epidemiology varies in different populations. Inusah *et al.* reported that the incidence of MSR ranges from 0.27 to 1.66/1000 people per year,[11] with a sustained reduction in the annual number of cases of MSR. Some have argued that this decline may be the result of changes in the inclusion criteria used for patients in randomized controlled trials (RCTs).[11] Ethical constraints often result in a significant proportion of patients suffering from active disease receiving highly efficacious medication. If this occurs, patients with a relatively less active form of MS could be included in RCTs,[12,13] eventually biasing the study outcomes. Other factors linked to a decline in the incidence reported in studies include advanced age at baseline (the "Will Rogers phenomenon") and disease duration.[12,13] The increasing homogeneity in RCT cohorts, coupled with a decrease in MSR at baseline, may result in further inflation of the change in MSR incidence reported in studies.[14] All of these factors must be considered when examining MSR and preventing adverse outcomes on patients, society, and the health-care sector.

Vitamin D levels

MSR risk is commonly predicted using serum levels of 25-hydroxyvitamin D [25(OH)D].[8,15,16] 25(OH)D is metabolized in the kidneys into 1,25-(OH)2D3, a hormonally active form of Vitamin D. Vitamin D levels are lower during MSR than during remission,[15,17,18] and higher serum levels of Vitamin D have been linked to a reduction in the risk of MSR.[15,19]

Simpson *et al.*[19] reported that a 10 nmol/L increase in Vitamin D concentration can reduce the risk of relapse by 9% and 34% among adult and pediatric MS patients, respectively. Mowry *et al.*[20] found that a 10 nmol/L change in Vitamin D concentration resulted in a 15% reduction in the risk of T2 brain lesions among MS patients. More recent studies have associated a serum level of Vitamin D <50 nmol/L with lower risk of MSR and disability.[21] Hence, Vitamin D supplementation is thought to reduce the risk of relapse.[15,22] A recent study by Martinelli *et al.*[15] reported that Vitamin D deficiency is a predictor of MS and MSR among CIS patients and a determinant of disease activity.[23] Runia *et al.*[16] reported that higher levels of Vitamin D in patients are correlated significantly with fewer MSRs,[24] and low Vitamin D levels appear to lead to increased disability among such patients.[24] A study of early and delayed interferon beta-1b (IFNβ-1b) treatment supports the association between MSR and serum Vitamin D levels. In that study, researchers measured the serum concentration of 25(OH)D at baseline and at 6, 12, and 24 months. Over a 5-year follow-up period, a 50 nmol/L increase in the level of 25(OH)D resulted in a 57% reduction in MSR prevalence.[5] A prospective case–control study involving 7 million US military personnel[25] showed that a 50 nmol/L increase in the level of 25(OH)D led to a 42% reduction in the number of MS and MSR cases. Two other studies showed that intake of fatty fish, a good source of Vitamin D, decreased the risk of MS,[26,27] but it is not clear if the same effect would be observed for MSR. Thus, there appears to be a relationship between MSR and Vitamin D levels.[23,24] Several studies aim to confirm this hypothesis and determine the optimal Vitamin D level.[28,29]

Further evidence of an involvement of Vitamin D is the fact that MSR is more prevalent at higher latitudes, where there is low sunlight intensity,[30-32] an effect that is more pronounced if the exposure occurs during childhood or adolescence.[24,33] Norval and Halliday[24] have shown that sunlight exposure improves outcome in a model of experimental autoimmune

encephalomyelitis (EAE). The association between sunlight and the risk of MS and MSR may also be an immunosuppressive effect.[25,26,34]

Sex

Researchers have reported that the prevalence of cerebellar relapse is more common among males and older patients with MS,[24,35] whereas female MS patients display more visual and sensory symptoms.[36,37] To examine these sex differences, gene expression profiles have been studied to assess the variation in MSR prevalence. Achiron and Gurevich[37] examined the sex-based effects of MSR and found a significant sex-based difference during the second MSR, as well as the onset and progression of MS. In particular, they showed that female patients experienced more rapid MSR compared to males. The authors identified the various biologic mechanisms that may influence this trend including increased immune activation and prominent inhibition of apoptosis in females.[38] This provides vital insights that could help health-care providers address and reduce MSR risk based on sex.

Gold and Voskuhl[39] have highlighted the possible role of hormones in the development and eventual relapse of MS. In studies in which male and female mice subjected to EAE were maintained under similar conditions, the latter were more susceptible to adverse symptoms. This trend was attributed at least in part to the processes that can result in the induction of the immune response, which are more responsive in female mice.[39] These results demonstrate the potential involvement of the immune system in the relapse and development of MS and the manner in which sex may contribute to variation in MSR prevalence.

Recently, researchers examined the role of Vitamin D in the development and relapse of MS in relation to sex hormones. Décard *et al.*[38] analyzed serum samples from MS patients with low levels of Vitamin D and found variation in levels associated with sex. Harbo *et al.*[40] argued that Vitamin D tends to mitigate MSR more strongly in female lymphocytes compared to male lymphocytes. Further, female mice demonstrate milder MS symptoms after being fed a diet rich in Vitamin D,[41] an effect attenuated following ovariectomy. This suggests a complex interplay between various factors that may affect MS development.[42]

There is growing evidence that estrogen levels in the body may influence neuroprotection. Research has shown that gray-matter atrophy is critical for the development and relapse of MS.[42] MacKenzie-Graham *et al.*[42] treated EAE mice using estrogen receptor (ER)-β ligand and ER-α ligand to examine the effects of estrogen in neuroprotection.[43] Histopathology and MRI results demonstrated the preservation and protection of Purkinje cells and gray matter following treatment.[43]

Several studies have detailed the manner in which high hormone levels in females can ameliorate the development and relapse of MS in clinical[41] and animal[38,41] studies. The therapeutic potential of hormone-based treatments in MS management relies on complex neuroprotective and immunomodulatory pathways. In several gynecologic studies, estriol has been regarded as one of the safest hormones for MSR management.[41] However, its use in men can lead to adverse side effects such as gynecomastia. Nonetheless, several beneficial immunological changes have been linked to the use of hormone-based interventions in MS care and have resulted in reduced symptomology and lower prevalence of MSR.[38,41] Further studies are required to examine the clinical utility of such interventions in different patient populations.

Pregnancy

Recent evidence suggests that many mothers experience a reduced prevalence of relapse and risk of MS during pregnancy, especially in the third trimester. However, a "rebound" effect may be observed in many cases following delivery.[44] Clinical predictors of postpartum MSR evaluated by logistic regression analysis have demonstrated the influence of hormonal changes.[36] Notably, pregnancy does not increase the risk of disability due to MSR.[44] Studies have shown that high levels of progesterone, estriol, and estradiol during pregnancy can increase the prevalence and risk of MSR; however, the precise mechanisms underlying the reduction of MSR risk remain unknown.[45,46]

Researchers have reported that pregnancy usually suppresses the mother's immune system, to prevent rejection of the fetus due to it bearing paternal antigens.[28,47,48] Therefore, several studies have investigated pregnancy as an immunomodulatory state that involves changes in the levels of different hormones and molecular agents such as progesterone, estriol, early pregnancy factor (EPF), and fetoprotein.[28,49] Low levels of estrogen and prolactin in the body have been associated with dysfunction of the T-helper 1 (Th1) cells that influence pro-inflammatory profiles in the body. In contrast, high estrogen levels during pregnancy result in dysfunction of Th2 cells. Progesterone tends to promote Th2 dysfunction while also minimizing EAE severity.[50,51] EPF results in beneficial outcomes, such as an increase in the numbers of Th2 cells, regulatory T-cells, and Th17 cells.[52,53] These hormonal changes that occur in a pregnant woman can influence the development of MS. Furthermore, they can affect the risk of MSR in women.[53,54] Ponsonby *et al.*[54] reported that pregnancy reduced the risk of the first MS attack and subsequent relapse. Nielsen *et al.*[55] showed that women with a reproductive history faced a lower risk of MSR compared with their childless counterparts, although selection bias may have influenced their results.

Effects of Genes and the Environment

Genes influence everything in humans, including susceptibility to diseases such as MS. Genetic variations affect susceptibility to MS and MSR. Family studies have shown that MSR prevalence is ~15%, and that MSR risk may be higher among first-degree relatives compared with other family members, an effect that tends to decrease with "genetic distance."[56] Several

researchers have shown that there is a genetic contribution to MSR that varies among different populations. These efforts have led to the identification of >110 genes that have critical roles in the development and relapse of MS.[57]

Due to a lack of reliable longitudinal data and shortage of prospective studies on MSR, several investigations on the link between genetics and MSR have thus far failed to identify the factors that can reliably predict the risk of MSR at the genomic level. Zhou *et al.*[56] undertook genome-wide association analyses in an attempt to identify different genetic variants that may influence and predict MSR. In total, they analyzed 449 DNA samples and clinical histories from various populations to determine the genetic differences that may influence MSR. The study identified a significant difference in one gene: low-density lipoprotein-related protein (*LRP2*). Conventionally, most genes that have been linked to MS development have been associated with the immune system, but *LRP2* is believed to be involved in development and processing information such as cognition and thoughts in the brain. The identification of *LRP2* as a reliable predictor of MSR offers exciting opportunities for developing targeted treatment options for MS and represents a critical finding that can provide important insights into the genetic and molecular drivers of MS. Other molecular factors that have been identified as potential predictors of MSR include the HLA-DRB1 locus as well as HLA-DQB1*0602 and HLA-DRB1*1501 alleles[41] and interleukin-7 receptor subunit alpha (IL7Ra) and ILR2a.[41]

It is widely believed that MS and MSR result from interactions between genetic and environmental factors.[58,59] The "genetic atlas" created by Didonna and Oksenberg[58] has helped researchers better understand the genetic component. Some environmental factors that have been identified include low levels of Vitamin D, smoking, Epstein–Barr virus infection,[58,59] viral infections during fetal development, exposure to ultraviolet rays, and dietary intake of salt. However, direct evidence showing how genetic factors interact with environmental factors to result in a higher risk of MSR in some patients is lacking.

Age

A recent comparison by Mansouri *et al.* based on collinear determinants of MSR showed that advanced age is closely linked to a decline in MSR activity compared with MS duration.[31] However, individuals aged >50 years are more likely to suffer from a wide range of conditions, including pneumonia, bacterial skin infections, septicemia, and urinary-tract infections,[60] which may exacerbate various health problems. Furthermore, these factors may lead to an increased risk of MSR among older adults.[60] The situation may worsen because older adults may experience reduced mobility and face difficulties in accessing health-care services,[60] leading to increased severity of MS symptoms and further complications.

While examining the age-dependent nature of MSR, some investigations have evaluated the potential role of inflammation,[21] which changes with age. Some researchers contend that inflammation is responsible for clinical relapses in relapsing–remitting MS and is associated with enhanced permeability of the blood–brain barrier with acute migration of peripheral immune cells into the CNS.[21,61]

Bacterial Infections

Pooled data from RCTs, systematic reviews, and meta-analyses have demonstrated a temporal correlation between viral/bacterial infections and MSR triggering.[28,47,48] Sibley *et al.*[48] conducted a study involving 170 MS patients to ascertain the environmental factors that might be important in MS and compare the prevalence of common viral infections.[49,50] During cumulative periods designated "at risk" (2 weeks before until 5 weeks after infection onset), the prevalence of exacerbation was almost threefold greater than that during periods designated "not at risk."[28] Approximately 27% of exacerbations were related to infections and 9% of infections were temporally related to exacerbations. The prevalence of common infections was approximately 20%–50% lower in MS patients than that in healthy controls and was progressively less in those with greater disability.[28] The prevalence of infection was significantly less in minimally disabled patients than in healthy controls. These results suggest that MS patients could have superior immune defense against common viruses, which is in agreement with studies examining the association between MSR prevalence and infectious disease episodes.[47,48]

Role of Medications in Multiple Sclerosis Relapse

In most instances, the symptoms of MSR are complex and vary between individuals.[56] The treatment of MSR is dependent on the physical status of the patient and symptom severity. Since the early 20th century, first-line treatment of acute MSR has been a 3 to 5-day course of corticosteroids,[48] which reduce CNS inflammation. Usually, corticosteroids are delivered (at home or in hospital) through intravenous infusion to elicit a rapid response.[41]

The US Food and Drug Administration (FDA) has also approved the drug methylprednisolone for MSR treatment, which can be administered along with corticosteroids for symptom relief. Alternatively, Acthar® gel and adrenocorticotropic hormone[48] are used if the patient cannot tolerate the effects of corticosteroids or if previous treatment options have failed. Studies have shown that plasmapheresis and intravenous administration of immunoglobulins can help in the management of MSR symptoms,[32] but these treatments have not been approved by the FDA.

Summary and Future Perspectives

Researchers have identified a wide range of factors that influence MSR.[21] These factors influence the prevalence and duration of MSR differently and affect the manner in which a

patient may respond to treatment. Thus, health-care providers must examine MS patients carefully and identify the possible causes of MSR to ensure effective management.[52] MSR can be diagnosed through a combination of physical examination, symptom appraisal, and neuroimaging. The outcomes of these assessments guide the management of MS and MSR.

Age, sex, pregnancy, serum levels of Vitamin D, interactions between genetic and environmental factors, and infectious diseases all appear to affect MSR. Most of these factors are modifiable and require the attention of patients and health-care providers if favorable outcomes are to be realized.

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Conflicts of interest

There are no conflicts of interest.

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