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Infections and Their Impact on Multiple Sclerosis

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ABSTRACT

Background: Multiple sclerosis (MS) is a prevalent central nervous system (CNS) disorder characterized by inflammation and demyelination of nerves. The incidence of this disease has markedly risen in diverse regions, including the Middle East. Any factor that alters the quality and quantity of immune system components or influences the migration of immune cells toward the CNS may contribute to MS development. Evidence suggests that paragenetic, genetic, and environmental factors may be involved in increasing MS risk. This study aimed to investigate the effect of various infections on MS incidence. .
Materials & Methods: This study included 475 MS patients and 260 healthy individuals from the Azeri population of East Azerbaijan province. Both groups filled out a questionnaire about their history of exposure to specific pathogens and infections before the age of 15.The relationship between a history of various infections and MS risk was examined.
Findings: *Mycoplasma pneumonia* infection was significantly more prevalent in MS patients than in healthy individuals ($p< .05$). MS patients were more likely to suffer from common colds ($p< .05$), but no significant difference was observed regarding other infectious diseases ($p> .05$). Additionally, the prevalence of chronic infections was higher among MS patients ($p< .05$).
Conclusion: *M.pneumoniae* infection, common colds, and chronic infections were significantly more common in MS patients than in healthy controls. However, no significant association was found between other infectious diseases and MS risk. These findings emphasize the possible role of specific pathogens in MS development, warranting further investigation into underlying mechanisms and contributing factors.

Keywords: Multiple sclerosis, Infections, Pneumonia, Common cold, Chronic

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Introduction

Multiple sclerosis (MS) is a prevalent central nervous system (CNS) disorder characterized by inflammation and demyelination of nerves [1]. The disease typically impacts individuals in their early adulthood, with the majority of patients being women [2]. The prevalence of this disease has significantly increased over the past few decades in various geographical areas, including the Middle East region [3]. Iran, as one of the countries in this region, has witnessed an increase in the number of MS patients. In 2017, the prevalence of this disease was reported to be 148 per 100,000 people in this country [4].

In MS, activated T lymphocytes and macrophages/monocytes cross the blood-brain barrier (BBB) and infiltrate the CNS, contributing to the development of the disease. Activated T cells encompass CD4+ T and CD8+ T cells [5]. In addition to these immune cells passing through the BBB, other immune cells contribute to the development of this disease. Targeting B lymphocytes may be effective in treating MS, suggesting that B cells also play a role in MS pathogenesis [6]. It seems that any factor that alters the quality or quantity of immune system components or influences the migration of immune cells (such as T cells) toward the CNS may be involved in increasing the risk of developing MS.

The precise etiology of this disease remains unclear; however, evidence supports the involvement of paragenetic, genetic, and environmental factors in elevating the risk of the disease incidence [7]. Among the genetic factors, we could mention polymorphisms in the vitamin D receptor gene [8] and the IL-10 promoter gene [9]. IL-10 is an anti-inflammatory and immune regulatory cytokine that suppresses Th-1 responses and inhibits the production of pro-inflammatory cytokines like TNF-α [12]. Meanwhile, environmental factors may include nutrition [10], adolescent obesity, nicotine exposure, and infections such as Epstein-Barr virus (EBV) [11]. Among the environmental factors, we could mention the role of various infections. Various infections could trigger the immune system through different mechanisms, leading to different qualitative and quantitative changes in multiple components of the immune system. Stimulation of the immune system and changes in its various components could lead to host immune activity against self, ultimately resulting in autoimmune diseases such as MS. For instance, certain infectious agents could generate and present amino acid sequences resembling host antigens. This mimicry could trigger an immune response against the host, leading to tissue damage [13].

Therefore, it seems necessary to study the relationship between different infections and the risk of developing MS by performing MS screening tests on people with certain infections to prevent further increase in the prevalence of MS worldwide.

Objectives: The objective of this study was to examine the influence of different infections on the incidence of MS in MS patients compared to healthy individuals in northwestern Iran. It is hoped that by implementing targeted MS screening approaches for patients with specific infections, the risk of MS will be reduced in Iran and the world.

Materials and Methods

This study included 475 MS patients and 260 unrelated healthy individuals (as controls) from the Azeri population of East Azerbaijan province. The study was conducted after obtaining the approval of the Ethics Committee of Tabriz University of Medical Sciences (IR.TBZMED.REC.1397.889). Participants comE pleted a questionnaire covering various ine fectious diseases, including parasitic, viral, and bacterial infections, focusing on patho-

Table1) Comparison of MS patients with healthy people in terms of different infections

	MS Patients (%)	Healthy Controls (%)	*P*-Value
Mycoplasma pneumoniae	21 (4.4)	1 (0.4)	002.
Epstein-Barr virus	8 (1.7)	1 (0.4)	126.
Parasitic infection	60 (12.6)	33 (12.7)	981.
Pneumonia	5 (1.1)	0 (0)	097.
Uterine infection	3 (0.6)	0 (0)	199.
Bladder infection	2 (0.4)	0 (0)	295.
Intestinal infection	2 (0.4)	0 (0)	295.
Eye infection	1 (0.2)	0 (0)	459.
Common cold (low*)	52 (11)	207 (79.6)	001.
Common cold (medium**)	269 (56.6)	42 (16.2)	001.
Common cold (high***)	154 (32.4)	11 (4.2)	001.
Chronic infections	114 (24)	3 (1.2)	001.
Total	475	260	

*Low; Catch a cold once a year or less.
**Medium; Catch a cold at most 2-3 times in a year.
***High; Catch a cold more than 3 times in a year.

gens likely contracted before age 15. The diagnosis of MS in patients was established by a neurologist using clinical and paraclinical criteria. The control subjects had no autoimmune diseases, neurological disorders, or inflammatory conditions, and there was no history of MS in their first-degree family.

Statistical analysis:

Statistical analysis was performed using SPSS software (version 27). Data analysis was performed by applying Chi-square test, with statistical significance set at a p value of less than 0.05.

Findings

The prevalence of *Mycoplasma pneumonia* infection was markedly higher among MS patients compared to healthy individuals ($p<.05$) (Table 1). Additionally, the common cold incidence was significantly higher among MS patients than among healthy individuals ($p< .05$). Conversely, most of the healthy individuals reported a lower incidence of the common cold compared to MS patients ($p<.05$). Moreover, no statistically significant difference was observed in the incidence of other infectious diseases between the two groups, including parasitic infections and EBV infection ($p>.05$). The incidence of chronic infections was significantly higher among MS patients than among healthy controls ($p<.05$).

Discussion

The diverse effects of environmental factors on MS risk have prompted researchers worldwide to investigate this issue in various studies to identify predisposing factors and, where feasible, implement modifications to prevent further increases in MS cases. This study was conducted to investigate the influence of different infections on the incidence of MS, given the elevated incidence of MS among individuals with a history of specific infections compared to those without such a history in Iran. Notably, a significant relationship was observed between the occurrence of certain infections and an increased

risk of developing MS.

This study findings indicated a significant association between *M. pneumoniae* infection and an elevated risk of MS. Among the MS patients studied, 21 individuals had a prior history of *M. pneumoniae* infection, while only one case with a history of this infection was observed among healthy individuals ($p< .05$). These results are consistent with the findings of another research conducted by Bahar et al. (2012) [14] to assess IgM and IgG antibodies against *M. pneumoniae* in 130 relapsing-remitting MS (RRMS) patients (85 in remission and 45 in relapse) as well as 50 sex- and age-matched controls. The findings indicated that women with MS were more likely to be seropositive for *Mycoplasma* antibodies compared to the control group. Mycoplasmas are the smallest, self-replicating, and free-living bacteria associated with various human diseases. Specifically, *M. pneumoniae* has been shown to attack the CNS and induce demyelination [15, 16]. This bacterium has been widely investigated due to its potential role in autoimmune and degenerative diseases. The connection between this bacterium and immune disorders was first discovered in the 1970s, and it was considered as a contributing factor to rheumatoid arthritis, MS, myalgic encephalomyelitis (ME), fibromyalgia, Crohn's disease, lupus, and diabetes. The type of disease caused by this bacterium seems to depend on the body cells it migrates to and attacks [17]. During M. pneumoniae infection, excessive immune reactions may lead to inappropriate immune responses against the lungs, liver, kidneys, red blood cells, smooth muscles, and especially neural tissue. Lesions in various locations of the nervous system may be associated with *M. pneumoniae* infections, such as meningitis, radiculitis, and acute encephalomyelitis. These unusual immune reactions due to *M. pneumoniae* infections suggest a potential link between *M. pneumoniae* and MS, making the presence of *M. pneumoniae* infection as a possible risk factor for developing MS [18].

The data obtained in this study demonstrated no significant association between a history of EBV infection and an increased risk of developing MS ($p> .05$). A history of this infection was reported by 1.7% of MS patients and 0.4% of healthy individuals. Despite the limited number of MS patients with a history of EBV infection in this study and the lack of a significant connection between EBV infection and MS risk, EBV may be associated with the risk of developing MS. Scientists have speculated about the potential role of EBV infection in increasing MS risk since 1980. Over time, various studies have confirmed this hypothesis, introducing EBV infection as a risk factor for MS [19, 20]. Notably, Abrahamyan et al. (2020) [19] investigated 901 patients with CIS (clinically isolated syndrome) or early RRMS. Antibodies against Epstein-Barr nuclear antigen (EBNA)-1 and viral capsid antigen (VCA) were measured in the patients' sera, ultimately revealing that all 901 (100%) patients were EBV-seropositive. Epstein-Barr virus (EBV), also known as human herpesvirus 4, is a widespread member of the herpesvirus family. It infects more than 90% of adults worldwide and remains permanently in the body, typically in B lymphocytes and cells lining the throat and pharynx [21]. While the precise biological mechanisms through which EBV may elevate the risk of MS remain to be fully clarified, there is ongoing scientific speculation regarding the underlying processes. One of these speculations is molecular mimicry. Various EBV antigens are targets of cross-reactive autoantibodies found in the body of MS patients. This cross-reactivity involves both humoral and cellular immune responses [22] and could partly explain the increased risk of MS caused by EBV. However, more studies are still needed on the biological mechanisms

through which EBV increases the risk of MS. Despite all these studies and speculations, this study found no significant relationship between a history of EBV infection and an increased risk of MS. The influence of EBV on susceptibility to MS is assessed through association with specific HLA genotypes, like the HLA-DRB1*15 allele [22]. Accordingly, the disparity in findings between this and other studies could be attributed to variations in the genotypic frequencies of this allele within the respective populations studied. The results of this study do not definitively rule out any link but emphasize the complexity of this relationship and the need to conduct more studies in this field.

The association between prior parasitic infections and the risk of MS was not statistically significant in this study, 12.6% (n=60) of MS patients and 12.7% (n=33) of healthy people reported a history of parasitic infections. A study conducted by Khalili et al. (2020) [23] identified a significant association between previous parasitic infections and an elevated risk of MS. In their investigation, 70 MS patients and 70 healthy controls, matched for relevant demographic and health variables, were assessed for serum anti-*Toxocara* IgG antibodies utilizing enzyme-linked immunosorbent assay (ELISA). According to the results, 28.6% of MS patients and 11.4% of healthy individuals had anti-*Toxocara* IgG in their serum. The observed difference was statistically significant, suggesting that a protective effect of *T. canis* against MS is improbable. Conversely, a study by Nicoletti et al. (2020) proposed that parasitic infections may exert a protective effect against MS and enhance the quality of life of individuals affected by MS [24]. In their investigation, researchers examined 129 MS patients and 287 healthy controls to assess the presence of specific *Toxoplasma gondii* IgG antibodies. Among the patients, 38 (29.5%) tested positive for anti-*T. gondii* antibodies in their blood, compared to 130 (45.4%) healthy individuals (p= .002). The results obtained suggest a possible protective role of parasitic infections against MS. The hygiene hypothesis proposes that parasitic infections may offer protective effects rather than inducing autoimmune conditions like MS. Substantial evidence supports this hypothesis, with epidemiological data serving as one of the key pieces of supporting information. MS prevalence is lower in areas where parasitic infections are more common. Another evidence supporting the hygiene hypothesis is scientific research on parasites and their interactions with the immune system. Recent research suggests that helminths and their immunomodulatory molecules may exert immunomodulatory effects, potentially mitigating the risk of MS [25]. These findings underscore the intricate interplay between parasitic infections and the immune system, providing valuable insights into the hygiene hypothesis. Therefore, given the differences in the results obtained in this field, larger-scale investigations are needed to unravel the complex interplay between parasitic infections and MS susceptibility.

The current study results indicated that individuals with MS were significantly more likely to suffer from common colds compared to healthy controls (p< .05). Among the MS patients studied, 154 (32.4%) patients reported a history of frequent common colds, whereas only 11 (4.2%) healthy individuals had a similar history. On the other hand, among healthy individuals, a larger proportion experienced fewer common colds. The results revealed that 52 (11%) MS patients and 207 (79.6%) healthy controls reported a history of infrequent common colds (p< .05). Also, 269 (56.6%) MS patients and 42 (16.2%) healthy people reported a history of moderate common colds (p< .05). The common cold is an upper respiratory tract infection primarily affecting the

nose. While more than two hundred types of viruses could cause the common cold, rhinoviruses (RVs) are the most common. RVs belong to the Enterovirus genus. Traditionally, they were classified into two species: RV-A and RV-B. However, recent advances in molecular techniques have led to the discovery of a novel species, RV-C [26]. RVs could trigger immune responses that may inadvertently contribute to MS pathogenesis. Also, dysregulation of the immune system, especially in chronic infections, could lead to auto-reactive attacks on myelin and oligodendrocytes in susceptible individuals [27]. Despite these findings, the association between rhinovirus infections and MS warrants further investigation. It is also important to mention that in this study, when people were asked about their history of colds, they considered the occurrence of any suspected cold symptoms as a cold. Consequently, the precise assessment of the association between a specific virus and MS risk remains elusive. To address this gap, further investigations employing molecular techniques are imperative.

In this study, individuals diagnosed with MS showed a significantly higher prevalence of chronic infections compared to the healthy control group ($p< .05$). Among the MS patients, 114 (24%) had a history of chronic infections, whereas this number was only 3 (1.2%) among the healthy control group. Abundant evidence suggests that chronic infections play a pivotal role in autoimmune and degenerative diseases [28]. Chronic infections may contribute to disease onset or impact disease progression. Moreover, research studies have identified specific pathogens as potential risk factors for MS, while some other pathogens have been suggested as protective factors against the development of MS. *Mycobacterium avium* subspecies paratuberculosis, *Chlamydia pneumoniae, M. pneumoniae,* and *Clostridium perfringens* type B could be mentioned among the possible pathogens that could trigger MS. On the other hand, *M. bovis* BCG and *Helicobacter pylori* may protect against MS [29]. Pathogens that trigger MS use different mechanisms of action to increase the risk of MS. For example, *C. pneumoniae* could change BBB permeability and cause infection and inflammation in the CNS [30].

Therefore, this pathogen could probably increase the risk of MS in this way. Furthermore, *C. perfringens* type B could impact myelin and oligodendrocytes via its epsilon toxin (a neurotoxin), warranting its classification as a possible pathogen associated with increased MS risk [31]. Microorganisms that provide protection against MS reduce the risk of developing the disease primarily by modulating the immune system through various mechanisms. For instance, BCG may reduce the risk of MS by diverting autoreactive T cells toward granulomas [32]. Also, *H. pylori* suppresses the immune system by suppressing Th1/Th17 cell responses and thus could be one of the possible protective factors against MS [33].

Therefore, given the influence of various pathogens on MS risk and their varying prevalence across different regions, comprehensive studies employing molecular techniques are warranted. These studies should focus on identifying species isolated from MS patients to enhance our understanding of the intricate interplay between pathogens and MS susceptibility.

This study had limitations, including a small sample size of MS patients in northwestern Iran. Additionally, instead of using specific tests to detect history of exposure to specific pathogens and infections, this study relied on a questionnaire filled out by participants. Furthermore, factors such as diet, vitamin D, and smoking were not taken into account. Future research should investigate the impact of other environmental factors, in addition to pathogens, on MS susceptibility.

Conclusion

Notably, *M. pneumoniae* infection, common colds, and chronic infections were significantly more prevalent in MS patients compared to healthy controls. Additionally, healthy individuals reported fewer common cold episodes than MS patients. However, no significant relationship was observed between other infectious diseases and MS risk. These findings highlight the possible role of specific pathogens in MS pathogenesis and warrant further exploration.

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Ethical permissions: The study was conducted after obtaining the approval of the Ethics Committee of Tabriz University of Medical Sciences (IR.TBZMED.REC.1397.889)

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