Does Epstein-Barr virus Cause Multiple Sclerosis?

Mohammad Amir Nasrollahpour*, Azam Azimi

Department of Education, University of Farhanghian, Iran

ABSTRACT

MS is a chronic autoimmune disease of the CNS. Until now there is no specific cause for MS, but EBV is the top candidate and this paper tested the theory that MS is caused by EBV. A 20 year old study of over 10 million soldiers shows the risk of MS increased 32 fold after infection with EBV but wasn’t increased with other infections. These findings can’t be explained by any known risk factor for MS and suggest EBV as the leading cause of MS.

Keywords: MS; EBV; Central Nervous System; Northern Hemisphere; vitamin D deficiency

INTRODUCTION

Multiple Sclerosis (MS) is a chronic autoimmune, inflammatory neurological disease of the central nervous system (CNS) [1,2]. MS attacks the myelinated axons in the CNS, destroying the myelin and the axons to varying degrees [3,4].

Multiple sclerosis (MS) is an acquired disabling neurological disease of young adults, affecting approximately 2.3 million people worldwide. It is most prevalent in North America (140 cases per 100,000) and Europe (108 cases per 100,000); the prevalence is lowest in sub-Saharan Africa (2.1 cases per 100,000) and East Asia (2.2 cases per 100,000) [5]. Overall, there are approximately 120,000 people with MS in the UK [6].

The past 20 years have seen remarkable advances in multiple sclerosis, including a better understanding of the fundamental immune drivers that mediate CNS demyelination and neurodegeneration, identification of risk genes, a more precise account of epidemiology and incidence, and the development of highly effective therapeutics.

Signs and symptoms of MS vary widely and depend on the amount of nerve damage and which nerves are affected. Some people with severe MS may lose the ability to walk independently or at all, while others may experience long periods of remission without any new symptoms.

There’s no cure for multiple sclerosis. However, treatments can help speed recovery from attacks, modify the course of the disease, and manage symptoms. The most common symptoms are tremors, vertigo, weakness, fatigue, stiffness, and painful spasms (Table 1).

Table 1: symptoms and signs of multiple sclerosis by site

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Signs</th>
<th>Established efficacy</th>
<th>Treatment</th>
<th>Speculative</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cerebrum</td>
<td>Cognitive impairment</td>
<td>Deficits in attention, reasoning, and executive function(early); dementia(late)</td>
<td>Cognitive training</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hemisensory and motor Affective (mainly depression) Epilepsy (rare) Focal cortical deficits (rare)</td>
<td>Upper motor neuron signs</td>
<td>Antidepressant drugs</td>
<td>Anticonvulsant drugs</td>
</tr>
</tbody>
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Corresponding author Mohammad Amir Nasrollahpour, Department of Education, University of Farhanghian, Iran, E-mail: mamirnt99@gmail.com

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It is generally accepted that autoimmune diseases like MS are because by the interaction between genetic and environmental factors.

**The Environmental Factor**

The global distribution of multiple sclerosis indicates that the Southern Hemisphere countries have fewer cases of MS than Northern Hemisphere countries (Figure 1) [7,8]. Multiple sclerosis is common in regions populated by northern Europeans but this distribution is modified by where individuals who are at risk of the disease live early in life. Several studies reported an increasing incidence of Multiple Sclerosis over time, although these data can be because of heightened awareness of the disease and new diagnostic techniques.

One of the reasons that western societies have more cases of the disease than others is maybe because of the large number of migrations that took place in those countries. Studies from South Africa [9], Hawaii [10], and the UK [11] correlate the risk of MS with the place of residence in childhood. Migrations from high risk to low risk regions in childhood are associated with reduced risk and from low to high prevalence parts of the world with an increased risk of developing multiple sclerosis by comparison with the population of origin. However, analysis based on a homogeneous Australian population shows no effect of age at migration, with 15 years as the point of stratification, suggesting that the risk of exposure spans a wider age range than was originally suggested [12].

Patients with multiple sclerosis report being infected with measles, mumps, rubella, and Epstein-Barr virus. In a population infection with Epstein-Barr virus increases the risk of developing...
multiple sclerosis in young adults. Some other environmental factors which trigger such as vitamin D deficiency, low sunlight, air pollutants, diet, radioactive rocks, cigarettes, geomagnetism, and toxins [13-15].

**Figure 1**: geography of multiple sclerosis and migrations. The five continents are depicted to show the medium prevalence of multiple sclerosis (orange), areas of exceptionally high frequency (red), and those with low rates (gray-blue). Major migration routes from the high-risk zone of northern Europe, especially small but in formative studies, are shown as dotted arrows. Study involving migrants from low-risk to high-risk zones are shown as solid arrows.

**The Genetics**

Multiple sclerosis has a familial recurrence rate of about 20%. Overall, the reduction in risk changes from 3% in first degree relatives (siblings, 5%; parents, 2%; and children, 2%), to 1% in second degree and third degree relatives (Figure 2) [16-19].

**Figure 2**: recurrence risks for multiple sclerosis in families Age-adjusted recurrence risks for different relatives of probands with multiple sclerosis, and degree of genetic sharing between relative and proband. Pooled data from population-based surveys. Error bars indicate the estimated 95% CLs.

Population based series of multiple sclerosis in twins from Canada and the UK show higher clinical concordance rates in monozygotic than in dizygotic pairs (25% vs 5%) [20,21]. In against, studies from France and Italy provide equivalent rates irrespective of zygosity [22,23].

**EBV**

Epstein-Barr virus (EBV), also known as human herpesvirus 4, is a member of the herpes virus family. It is one of the most common human viruses. EBV is found all over the world. EBV spreads most commonly through bodily fluids, primarily saliva. EBV can cause infectious mononucleosis, also called mono, and other illnesses.

Epstein-Barr virus (EBV) was discovered 60 years ago by examining electron micrographs of cells cultured from Burkitt’s lymphoma, a childhood tumor that is common in sub-Saharan Africa, where its unusual geographical distribution matches that of holoendemic malaria indicating a viral etiology. However, far from showing a restricted distribution, EBV was found to be widespread in all human populations and to persist in the vast majority of individuals as a lifelong, asymptomatic infection of the B-lymphocyte pool [24].

The demyelination in the brain and spinal cord is an immune mediated process [25] possibly triggered by a viral infection [26]. Among the putative causal agents, the top candidate is Epstein-Barr virus (EBV) [27]. A causal role of EBV is supported by the increased MS risk after infectious mononucleosis [28], elevated serum antibody titers against EBV nuclear antigens (EBNAs) [29], and the presence of EBV in MS demyelinated lesions reported in some [30-32], but not all [33], pathological studies. Evidence of causality, however, remains inconclusive. Causality implies that some individuals who developed MS after EBV infection would not have developed MS if they had not been infected with EBV [34].

A considerable amount of evidence linking Epstein-Barr virus (EBV) infection to risk and disease progression in multiple sclerosis (MS) builds on the background of the virus and its interactions with the human host. There is strong evidence that people with MS are more likely to report a history of infectious mononucleosis (thought to represent initial EBV infection at an older age), and higher titers of EBV-specific antibodies are associated with an increased risk of developing MS [35].

**MATERIAL AND METHODS**

**Source Population**

The study was conducted among personnel on active duty in the U.S military. In 2019, 45.7% of the members were 25 years or younger, and most were male (83.1%). Most individuals reported themselves as white (68.8%). Black or African American individuals represented 17.2%, while Asian, Native Hawaiian or Other Pacific Islander, Indian or Alaska Native, and Multi-racial individuals made up 4.7, 1.2, 1.1, and 3.0%, respectively. Serum from the examinations is cataloged and stored in the Department of Defense Serum Repository (DoDSR) in Silver Spring, Maryland. Each sample is assigned a unique ID code and stored at -30°C. As of 2021, the DoDSR contained over 62 million samples collected from over 10 million active and reserve duty members. The DoDSR is overseen by the Armed Forces Health Surveillance Branch (AFHSB), which makes samples available for research studies that are conducted by mili-
tary investigators or in collaboration with military investigators and have obtained approval after a thorough scientific and military relevance review by scientists. The covariate data on MS cases and matched controls used in this study come from the DMSS, including age, sex, race/ethnicity, branch of military service, dates of serum sample collection, and state of residence at the time of entry into active duty (Figure 3).

Figure 3: Flow-chart of the study.

**Study Design**

This is a prospective, nested case control study design that utilizes risk set sampling. This is a common and efficient study design when there is a large cohort, and the purpose of the study is to determine whether the disease of interest is related to a yet unmeasured biomarker. Controls are randomly selected but matched to the cases for key covariates to increase efficiency. This design provides an unbiased estimate of the rate ratio that would have been observed had all individuals and serum samples been included (Figure 4).

**Epstein-Barr virus (EBV) and Human Cytomegalovirus (CMV)**

Global All the serological assays were performed and interpreted without knowledge of the case or control status of each sample. For EBV and CMV serology, serum samples were sent to the laboratory performing the assays without identification of case or control status and arranged in triplets; each triplet included a case serum and the two corresponding matched control sera in random order. Further, blind quality control samples consisting of triplicate aliquots of the same serum were interspersed with the study samples to monitor within and between batch coefficients of variation Residual serum samples.

**RESULTS**

Throughout a 20 year collaboration with the US military, they have identified cases of MS in a cohort composed of active duty US military personnel between 1993 and 2013, a racially diverse population of >10 million individuals [34]. They documented 955 incident MS cases among active duty military personnel including 315 cases from our preliminary study [36]. Behavioral, environmental, or personal characteristics may correlate with a predisposition to both infection and MS. To assess this possibility, they measured antibodies against cytomegalovirus (CMV), a herpes virus that, like EBV, is transmitted through the saliva. CMV displays socioeconomic and racial/ethnic disparities in age at infection in the US population [37] similar to those of EBV [38], thus constituting an ideal negative control [39]. Among those who were CMV-negative at baseline, seroconversion for CMV occurred at a similar rate in those who later developed MS and those who did not, MS risk was lower among CMV positive than among CMV-negative individuals, consistent with a previous report and with suggestions that the immune response to CMV attenuates the adverse effects of EBV [40].

**DISCUSSION**

A causal interpretation of results requires ruling out the possibility that systematic differences between individuals who were seroconverted and those who remained EBV-negative explain the results. These differences can be grouped into two categories: (i) confounding by known or unknown factors and (ii) reverse causation.

Confounding by known factors is ruled out by the strength of the association. To explain a 32 fold increase in MS risk, any confounder would have to confer a >60 fold increase in the risk of EBV seroconversion and a >60 fold risk of MS [41]. None of the known or suspected risk factors for MS has such strong associations. The next strongest known risk factor for MS, homozygosity for the HLA-DR15 allele, which confers a threefold increase in MS risk [42], is not associated with EBV positivity [43] and thus cannot explain the EBV-MS association. Rather, there is epidemiological [44] and experimental [45] evidence that EBV infection and HLA-DR15 may act synergistically in causing MS. Environmental factors are also far too weak to materially confound the EBV-MS association [46]. The existence of a still unknown factor that increases the risk of both EBV infection and MS by >60 fold is rather implausible and there are no good candidates, even hypothetical ones. This conclusion would be robust even in the very unlikely case that EBV seroconversion in one of the MS cases was a false positive result, in which case EBV infection would confer a 16 fold increase in MS risk.

Reverse causation could occur if the immune dysregulation...
during the preclinical phase of MS increases the susceptibility to EBV infection. In our agnostic search of the entire human virome during the preclinical phase of MS, we did not find other Systematic differences in the antibody response to any pathogen except EBV that was related to previous infections in MS cases and controls, which makes it unlikely that immune dysregulation during this phase increases susceptibility to infections. This is consistent with previous studies reporting no difference in the frequency of infections in the 5 years preceding MS onset [47] or in individuals with untreated MS [48–52]. Collectively, these findings strongly suggest that the occurrence of EBV infection, detectable by the elicited immune response, is a cause and not a consequence of MS.

CONCLUSION

The extremely low MS risk in EBV-negative individuals suggests that by far most MS cases are caused by EBV and could thus potentially be prevented by a suitable vaccine. The addition of MS to the list of diseases that an EBV vaccine could target strengthens the rationale to accelerate ongoing research with the primary goal of preventing infectious mononucleosis and post-transplantation lymphoproliferative disease.

One of the most effective treatments for MS is anti-CD20 monoclonal antibodies, which deplete circulating memory B cells, the primary site of persistent latent EBV infection. This, and preliminary results obtained with EBV-specific T cell therapy, suggest that EBV, in addition to causing MS, contributes to MS clinical course, which could thus be potentially modified by antivirals. Directly targeting EBV could have major advantages compared with anti-CD20–based therapies, which have to be administered by intravenous infusion and may increase the risk of infections.

REFERENCES


