Review Article

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The Link Between Epstein-Barr Virus and Multiple Sclerosis: Recent Scientific Evidence

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ABSTRACT

Epstein-Barr virus has been debated over the previous years to be linked to the pathophysiology of multiple sclerosis and medical research has proposed this link. This review presents an overview of research investigating the potential mechanisms underlying the role of the Epstein-Barr virus in multiple sclerosis, particularly the immunological and genetic links between the two, and potential treatment options for multiple sclerosis in relation to the Epstein-Barr virus for future reference. To conduct a literature search, the electronic databases Medline (Ovid), PubMed, Scopus, Web of Science, clinicaltrials.gov, and clinicaltrialsregister.eu were used. Evidence from research shows that the primary two possible immunological mechanisms by which the Epstein-Barr virus infection could increase the risk of developing multiple sclerosis are molecular mimicry or direct central nervous system infection. Studies exploring the genetic link between the virus and multiple sclerosis show that the interaction of the Epstein-Barr virus with the multiple sclerosis genetic risk factors HLA allele DRB1*15:01 and allele B*07 increases the risk of multiple sclerosis. Due to the extensive immunological association between the Epstein-Barr virus and multiple sclerosis, it is vital to introduce treatment methods that focus on cell-Epstein-Barr virus targets as a potential treatment. Research shows that this is the target of many clinical trials. The exploration of new treatments, including current clinical trials has revealed that therapies focusing on B cell depletion, anti-Epstein-Barr virus antibodies, and antiviral compounds could facilitate to lower the Epstein-Barr virus viral load and thereby decrease the burden of Epstein-Barr virus-induced immunopathology in multiple sclerosis.

INTRODUCTION

Multiple sclerosis (MS) is a disabling neurological disease of the central nervous system (CNS) comprised of a dysfunctional immune system. It commonly affects young individuals between twenty and forty years of age [1-3]. It is characterised by inflammation, demyelination, breakdown of the blood-brain barrier, lesion formation, and axonal damage [1,4]. Over time, the attack of autoreactive lymphocytes on the myelin sheath of the CNS lead to damage which can cause a wide range of symptoms and eventually lead to disability. Inflammation is present in all forms of MS where neurodegeneration and active demyelination occur [3]. MS has been proposed to be associated with multiple genetic, environmental, and neuroimmune factors [4]. Medical research throughout the years has proposed that infection with Epstein-Barr virus (EBV) could play a primary role in the pathophysiology of MS [1,5].

EBV, also known as human herpesvirus 4 is a memory B cell tropic virus and a member of the herpes virus family. Research shows that genome-wide association studies (GWAS) have identified greater than two hundred susceptibility loci which accounts for a large ratio of the heritability of MS. According to a study by Afrasiabi A, et al. although EBV is not sufficient for the development of MS, it has been identified as necessary [6]. Primary EBV infection most commonly occurs in children of a young age and presents asymptomatically. Nevertheless, EBV infection occurring in adolescence or early adulthood is more often associated with clinical symptoms and is manifested as infectious mononucleosis (IM) in approximately 30% to 40% of infected individuals. Although evidence of the causality of MS from EBV remains inconclusive, it is supported by the increased risk in MS after IM, the presence of EBV

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in MS demyelinated lesions, and by the elevated serum antibody titres against EBV nuclear antigens (EBNAs) [7]. Due to the varying conclusions (from studies over the previous years) regarding the link between EBV and MS, it is critical to consider the current knowledge on the topic and explore future management and treatment options for patients. This review focuses on an overview of research investigating the potential mechanisms underlying the role of EBV in MS, particularly the immunological and genetic links between them. Potential new treatment options for MS in relation to EBV for future reference will also be explored.

METHODS

Search Strategy and Selection Criteria

The electronic databases Medline (Ovid), PubMed, Scopus, Web of Science, clinicaltrials.gov, and clinicaltrialsregister.eu were used to conduct the search. Medline (Ovid) and Scopus were searched using the terms 'Epstein-Barr virus', 'Herpesvirus 4, human' and 'multiple sclerosis'. PubMed was searched using the terms 'Epstein-Barr virus' and 'multiple sclerosis' and Web of Science was searched using the terms 'human herpesvirus 4' and 'multiple sclerosis'.

Letters, opinion pieces and studies without any authors were excluded from this review search. Additionally, information from reviews and systematic reviews was excluded when writing the body of this review. Furthermore, case reports, case series, information from conference meetings, clinical trials and randomised control trials (RCTs), and languages other than English were all part of the inclusion criteria for the searches.

Immunological Link Between Epstein-Barr Virus and Multiple Sclerosis

Many studies have been conducted in recent years that attempt to explain the immunological link between EBV and MS. Previous studies, specifically a case-control study of high external validity, with a large sample size of 670 individuals with MS and 670 control cases, have postulated two possible mechanisms by which EBV infection could increase the risk of developing MS. These mechanisms are molecular mimicry or through direct CNS infection [8,9]. According to the mechanism of molecular mimicry between EBV gene products and MS autoantigens, the T cells prepared by exposure to EBV antigens (primarily Epstein-Barr Nuclear Antigen 1 (EBNA1)) cross-react with and attack CNS antigens. This is evident through increased activation of autoreactive CD4+ T cells identified by studies, which can cross-react with self-peptides and EBV peptides and attack proteins in the white matter of the brain [10]. With regards to the latter mechanism by which EBV infection can increase MS risk, several studies (of which many were conducted on autopsied human brain tissue) have reported the detection of EBV-infected plasma cells and B cells in the brain of MS patients [10-17]. Along with this, the defective elimination of EBV-infected autoreactive B cells by CD8+ T cells can result in its accumulation in the CNS and consequently lead to inflammation, demyelination and axonal destruction and drive MS pathogenesis [10,18,19]. This is further supported by the results of a study by Cencioni MT et al. which investigated the response of a subpopulation of effector CD8+ T cells to EBV in MS patients. From their study, it was plausible to propose that the persistent chronic inflammation which underlies the rapid progression of MS is because of the inability of CD8+ CD57+ T cells to clear the EBV infection in the CNS [19,20].

Furthermore, the dysfunctional CD8+ T cell response to EBV antigens at the onset of and at subsequent stages of MS, is further supported by another comprehensive study by Pender MP et al. Normally EBV is continuously being reactivated in the tonsil through the shedding of virions into saliva. This process is normally regulated by lytic-specific cytotoxic CD8+ T cells, however, in MS the dysfunctional CD8+ T-cell control of EBV reactivation consequently increases the production of infectious virions through increased oral shedding. This can subsequently increase infection of new naïve B cells which go on to become blast cells in a new cycle of infection, hence has amplified the damaging effects on MS patients [21]. The study did, however, only analyse the effects on females, hence is a limitation as it is not representative of the wider population. Furthermore, in support of other studies, an animal study conducted on rabbits revealed that primary peripheral EBV infection can lead to CNS infection and neuroinflammation when the virus traverses the CNS [22]. B lymphocytes were identified as the infected cells within the brain [10,22,23]. Additionally, the CNS of animals with EBV developed inflammatory cellular aggregates containing compact clusters of macrophages surrounded by reactive astrocytes and T and B lymphocytes. Peripheral EBV infection was found to activate temporal changes in the expression of cytokines and latent viral transcripts in the brain. These findings depict a model to understand the contribution of viral mechanisms like EBV to the development of MS [22]. Along with immunological links, genetic links have also been revealed to be a significant contributor to the pathogenesis of MS concerning EBV infection.

Genetic Link Between Epstein-Barr Virus and Multiple Sclerosis

Multiple studies have suggested that genetic links may be significant in the risk of MS in association with EBV infection. The association between these two factors may initially be explained by the common genetic determinant of a specific genotype that increases the risk of both MS and EBV infection. Numerous epidemiological studies have identified human leukocyte antigen (HLA) alleles that correlate with an increased risk of developing MS and have shown that allelic variations in the receptor could cause the effect of EBV infection of B cells [24-26]. HLA allele DRB1*15:01 (HLA-DR15) is confirmed as the strongest genetic risk factor of MS according to genome-wide association studies. However, in primary EBV infection, the EBV glycoprotein g42 has been found to interact with this genetic risk factor, hence increasing the risk of MS by seven-fold. Studies have shown that EBV infection in the context of influencing the primary genetic risk factor for MS leads to decreased EBV-specific immune control, thus supporting the priming of hyper-reactive and cross-reactive T cells (HLA-DRB1*15:01 restricted EBNA1 specific CD4+ T cells) which go on to activate myeloid cells with proinflammatory cytokines to initiate myelin damage [9,27-29] Additionally, a study using post-mortem brain tissue identified genes related to T cell activation, B cell growth and differentiation, cytotoxic cell-mediated immunity, pathogen recognition, and leukocyte recruitment expressed at differing levels in the majority of the MS brain immune infiltrates. The study's use of twenty-three post-mortem brain tissues ensured the validity of the results [15]. Furthermore, using a quantitative PCR, a cross-sectional study detected EBV DNA and RNA in the peripheral blood of patients with MS and it was conveyed that EBV DNA increased before and during clinical relapse in paired samples, which was suggestive of reactivation of EBV preceding a relapse of the condition. Although it is not an RCT, the study's use of cross-sectional methodology is a strength since cross-sectional and serological studies have been stated as the methodologies that yield some of the best evidence linking EBV and MS [30]. Furthermore,

along with HLA-DR15, a different MS risk allele, B*07 (HLA-B*07+), which belongs to the same HLA haplotype that carries the HLA-DRB1*15 allele, has recently been identified in EBV infection in MS patients. Its association has been supported by the results of a study by Agostini S, et al. which identified that the patients with the highest EBV viral loads were those carrying the B*07 allele in the presence of the allele DRB1*15:01 and in the absence of the protective allele A*02 [28]. In conclusion, multiple reliable studies have represented the genetic link between EBV and MS. The current knowledge on the immunological and genetic aspects of the pathogenesis and progression of MS in EBV-affected patients serve as a gateway to the development and utilisation of new treatments for MS patients.

Proposed Treatment Options for the Future

Due to the extensive immunological association between EBV and MS, many clinical trials are focusing on cell-EBV targets as a potential treatment. Along with current treatment for MS patients, multiple new treatment approaches and undergoing clinical trials are being considered to address the treatment of MS with regards to EBV. The control of EBV infection in MS can potentially be achieved by anti-EBV antibodies and targeting viral pathways, antiviral compounds, and cell-based immunotherapies. The current treatments for MS have generalised effects on the immune system but fail to specifically target EBV, thus many recent clinical trials focus on this treatment gap. Ongoing clinical trials using EBV-specific adoptive T-cell therapy will increase the knowledge on whether the implementation of immune control of EBV will yield beneficial results in patients with progressive or early MS. Atara Biotherapeutics, a leading allogenic T-cell immunotherapy company, is investigating an off-the-shelf allogenic T-cell immunotherapy known as ATA188. This immunotherapy, which is entering phase II of an RCT, is designed to target EBV antigens specific for the potential treatment of progressive forms of MS by crossing the blood-brain-barrier (BBB) and attacking plasma and B cells specifically expressing EBV surface proteins [10,23] Another current prospective non-interventional study (that has not yet started recruiting participants) aims to investigate whether B cells infected by different EBV genotypes are involved in migration across the BBB and how the immunomodulatory drug Ozanimod may interfere with this mechanism. By investigating the ability of ozanimod to reduce the cytokine-mediated breakdown of the BBB and the migration of EBV-infected B cells in MS, this drug can have potential future implications on the effective treatment of MS [31] Furthermore, the results of a prospective clinical trial that sought to investigate the feasibility and safety of treating progressive MS patients with autologous EBV-specific T cell therapy, conveyed a significant relationship between clinical response and EBV reactivity and polyfunctionality of the T cell product. This suggested that the T cell therapy may have contributed to the clinical benefit. All participants of the study that received T cells with strong EBV reactivity experienced clinical improvement and the reason for this was postulated to be from the termination of EBV-infected B cells in the CNS by adoptively transferred cytotoxic CD8+ T cells, which subsequently prevented further autoimmune attacks on the CNS, enabling neurological recovery through remyelination and dendritic and axonal sprouting. Since T cells have access to all CNS compartments, T cell therapy targeting only EBV-infected B cells is a treatment modality that can yield a safe and durable clinical outcome [32,33]. As previously mentioned, the continuous reactivation of EBV in the tonsil through the oral shedding of virions into saliva increases the production of infectious virions. To address this issue, a current phase II type A proof-of-concept study in patients with relapsing-remitting multiple sclerosis is underway. This study aims to explore the effect of the antiviral drug famciclovir on EBV shedding in the saliva of patients with MS thus serves as a potential treatment to decrease oral EBV shedding in the saliva, hence decreasing the damaging effects of MS [34]. In conclusion, therapies focusing on B cell depletion, anti-EBV antibodies, and antiviral compounds could facilitate to lower the EBV load, hence decrease the burden of EBV-induced immunopathology in MS, potentially with greater efficacy than other drugs.

CONCLUSION

Analysis of recent literature has identified multiple immunological and genetic links between MS and EBV and current clinical trials have shown new treatments that could potentially sever the link between these two conditions. Research has identified that the primary two possible immunological mechanisms by which EBV infection could increase the risk of developing MS are molecular mimicry or direct CNS infection. Additionally, studies exploring the genetic link between the two variables have shown that EBV interaction with the MS genetic risk factors HLA allele DRB1*15:01 and allele B*07 increases the risk of MS. The exploration of new treatments has revealed that therapies focusing on B cell depletion, anti-EBV antibodies, and antiviral compounds could facilitate in lowering the EBV load and thereby decrease the burden of EBV-induced immunopathology in MS. Due to the lack of RCTs investigating the link between EBV and MS, it is recommended that future studies adopt this methodology to increase the quality of the evidence.

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