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Chapter

Epstein-Barr Virus in Multiple Sclerosis

Gulfaraz Khan and Asma Hassani

Abstract

Multiple sclerosis (MS) is a chronic inflammatory disease of the central nervous system in which the body's immune system is abnormally directed towards the myelin sheaths covering the nerve fibers. What triggers the neuroinflammation and autoimmune destruction of the myelin sheaths remains unknown. However, it is widely accepted that susceptibility depends on a combination of genetic and environmental factors and their interactions. With little chance of influencing genetic predisposition, the importance of identifying risk factors which could be modulated to either prevent the on-set of MS or to ameliorate the course of the disease, is an attractive alternative. An accumulating body of evidence, including our own recent study involving over 1000 MS and non-MS samples, indicates that Epstein-Barr virus (EBV), a common herpesvirus, could be involved. In this chapter, we review the studies linking EBV to MS and propose an explanation by which this common virus could be involved in the pathogenesis of MS.

Keywords: multiple sclerosis, autoimmunity, neuroinflammation, Epstein-Barr virus, seroepidemiological evidence, postmortem studies

1. Introduction

Multiple sclerosis (MS) is a progressive disease in which multiple regions in the brain, spinal cord and optic nerve undergo myelin destruction or demyelination. It is believed that an aberrant immune response mistakenly attacks the myelin sheaths in the central nervous system (CNS) resulting in the formation of focal demyelinated plaques; the hallmark of MS [1]. In spite of extensive search, the identity of the factor(s) that triggers the immune assault against the myelin remains elusive. It is generally accepted that MS is a complex disease and most likely involves both genetic and environmental factors [2]. Although no single gene has been identified to be responsible in the development of MS, certain HLA haplotypes, such as HLA-DRB1 have been shown be associated with MS susceptibility [3]. Furthermore, the fact that MS is more prevalent in certain races such as Caucasians [4, 5] and incidence rates are increasing in some ethnic groups such as blacks [6, 7] supports the involvement of genes in the development of MS. Although the risk of MS is significantly higher in individuals with first-degree relatives with MS, this still does not explain the occurrence of MS in majority of cases. In fact, MS concordance in monozygotic twins is only around 25% [8, 9]. This clearly indicates that environmental factors play a key role in the development of MS in genetically predisposed individuals.

1.1 Environmental risk factors for MS

In support of the above observations, MS prevalence has been reported to be higher in the northern hemisphere, but lower towards the equator. However, recent studies indicate that this pattern of distribution, known as the latitudinal gradient, is changing in some countries such as Norway and USA [10–12]. Moreover, migration studies indicate that the increasing burden of MS is due to exposure to certain factors in the environment, which may account for a bigger proportion of MS risk than genetic factors. These studies show that leaving countries with high MS incidence prior to reaching adolescence, to regions with low MS incidence, confers protection against developing the disease [13]. Similarly, migrating in the opposite direction is linked to increased risk of developing MS [14–16]. These protective and MS predisposing effects have been shown to occur in a single generation, and this is highly unlikely to be due to effects of genes which usually manifest on longer periods of time [17].

Additionally, exposure to specific environmental agents at a young age seems to be critical in shaping the risk of developing MS [18]. The past few decades have seen a rapid accumulation of epidemiological data pointing to a number of different environmental factors that could potentially be involved in MS pathogenesis. However, no single causative agent has yet been unequivocally shown to be central to MS development [19]. Environmental risk factors associated with MS include sunlight exposure and serum levels of vitamin D, smoking, obesity, female sex hormones, and infection with Epstein-Barr virus (EBV) [20–22]. Among these factors, infection with EBV, particularly when manifested as infectious mononucleosis (IM), appears to have the most significant and consistent association with the risk of developing MS [23].

1.2 Infectious risk factors for MS: Hygiene hypothesis

The notion that an infectious agent is involved in the pathogenesis of MS is not new. A number of observations, including MS outbreak in the Faroes islands during World War II, which coincided with the British occupation of the islands [24], and MS occurrence in clustering fashion (e.g. familial clustering of MS), suggested an infectious cause for MS [17]. The hygiene hypothesis was used to provide an explanation for such involvement [21], assuming that certain infections occurring during the first few years of life can protect against MS, whereas exposure to the same infections later in life, predisposes to MS [25]. The hygiene hypothesis also partly explained the geographical distribution of MS, in that it is less common in tropical regions that are known to be endemic to certain microbial infections. In these areas, children tend to acquire infections very early in life [26, 27]. Similarly, MS incidence seems to rise in tropical regions [28] that have witnessed improved feasibility of vaccines and antibiotics and enhanced sanitary conditions which have led to decreased childhood infections [29–31]. However, some epidemiological observations such as the finding that the risk of MS in individuals who have never been exposed to EBV is 10 fold lower than in those who were exposed to childhood EBV infection [32], cannot be explained by the hygiene hypothesis.

2. Epstein-Barr virus (EBV)

EBV is a common human herpesvirus, infecting over 90% of the population worldwide [33]. Generally, EBV infection is considered to be one of the early asymptomatic childhood infections and in the vast majority of the infected individuals, the virus persists for life without causing disease. Bizarrely, if primary infection is delayed until adolescence, as commonly noted in developed countries, the virus can

cause an acute self-limiting symptomatic infection known as infectious mononucleosis (IM) [34]. Importantly, EBV has oncogenic properties and in a very small percentage of individuals, the virus can induce life-threatening lymphoid and epithelial malignancies, accounting for approximately 150,000 deaths annually [35, 36].

EBV is transmitted from person to person through salivary exchange. However, the details of the early steps in EBV infection remain unclear. Two models have been proposed. In the first model, it is suggested that EBV initially infects tonsillar epithelial cells where it undergoes lytic replication with subsequent infection of B-lymphocytes. In the second model, it is suggested that EBV directly infects B-lymphocytes without the involvement of epithelial cells [37, 38]. Whatever the initial cellular target, one thing is fairly well-established; the cellular site of long-term EBV persistence is B-lymphocytes [39, 40]. These cells can be transformed and immortalized by EBV when grown in *in vitro* cultures, forming what are known as lymphoblastoid cell lines (LCLs). In LCLs, a number of viral latent products, namely 2 EBV encoded RNAs (EBER 1 and 2), 6 EBV nuclear antigens (EBNAs 1, 2, 3A, 3B, 3C and LP) and 3 EBV latent membrane proteins (LMPs 1, 2A and 2B) are expressed [33]. The expression of these latent products in infected cells is referred to as EBV latency III program and is typically observed in EBV associated post-transplant lymphomas [41] and in IM [42]. When EBERs, EBNA-1, LMP1 and LMP2 are expressed, it is known as latency II, typically seen in EBV associated Hodgkin's lymphoma. In latency I, only EBERs and EBNA-1 are expressed, as seen in Burkitt's lymphoma. In latently infected asymptomatic EBV carriers (>90% of the population), infected B cells express EBERs only [43]. Since no viral proteins are expressed in these cells, the virus can remain out of the radar of the host immune system. This strategy allows the virus to be dormant, but still dangerous. Moreover, the virus utilizes an array of viral encoded miRNAs to target immune associated mRNAs, aiding its escape from host defenses [44, 45]. Thus, EBV has evolved to be a master manipulator of the immune system, ensuring its persistence for the life of its host, even in the face of a competent immune system.

Beside the latent infection described above, a lytic infection can occasionally occur resulting in production of new virions. The expression of the immediate early lytic protein BZLF1 signals the beginning of the lytic cycle. Whether it is latent or lytic infection, an efficiently functioning immune system is essential to keep EBV infection under control and maintain a homeostatic virus-host relationship [46]. Thus, any disruption of the intricate connection between EBV and the immune system can lead to serious health conditions, for instance EBV-induced malignancies and some autoimmune disorders such as MS. Based on an accumulating body of evidence from epidemiological, serological and postmortem studies, it is now widely believed that EBV is associated, directly or indirectly in the pathogenesis of MS [20–22]. However, the details of how EBV induces or promotes an aberrant immune response against myelin self-antigens in MS remain unknown.

3. Epidemiological link between EBV and MS

A considerable amount of literature has been published on the link between the epidemiology of MS and EBV infection. Early reports consistently showed higher prevalence of EBV infection in MS patients compared to the general population [47, 48]. This difference was particularly pronounced in the pediatric cohort, where almost 100% of children with MS were EBV seropositive compared to 72% matched controls [49–52]. Consistent with these findings, MS risk was found to diminish in individuals who have never been exposed to EBV infection (the odds ratio of developing MS is 0.06 in a seronegative person compared to 13.5 in an EBV seropositive person). Furthermore, continuing to be EBV seronegative keeps MS risk to about

10-fold lower than those who seroconvert [53] and about 20-fold less than those with a history of IM, the primary symptomatic EBV infection [32]. These reports suggest that the risk of MS rises in EBV-seronegative individuals soon after they seroconvert as confirmed by a nested case–control study on 305 MS cases and 610 controls [54].

Interestingly, IM has a strikingly similar distribution to that of MS [55]. Moreover, females report IM symptoms earlier (more prolonged), more frequently, and with more severity than their male counterparts. Females also tend to have higher anti-EBV titers and are believed to mount stronger response against EBV [56, 57]. In demonstration of the correlation between IM and the risk of MS, a case–control study found that history of IM increases the risk of developing a CNS demyelinating disease, particularly in genetically susceptible individuals who are HLA-DRB1*1501 positive [58]. In support of these results, a meta-analysis of 14 case–control and longitudinal studies reported that history of IM significantly increased the risk of MS by over 2 folds [59]. Furthermore, this increased risk persists for at least 30 years post EBV infection [60], suggesting that symptomatic EBV infection manifested as IM may be a prerequisite to developing the autoimmune response associated with MS [61].

4. Serological link between EBV and MS

More evidence has been brought to light by serological studies investigating antibody response against EBV antigens in MS patients compared to that in controls. One of the most consist piece of evidence is the finding of elevated antibody titers against EBNA-1 antigen in the blood, both pre- and post-onset of the disease [62–65]. Indeed, individuals with clinically isolated syndromes (CIS) are more likely to develop definite MS when they experience elevated antibody response to EBNA-1 [66, 67]. Furthermore, serum levels of anti-EBV capsid antigen (VCA) together with anti-EBNA-1 IgG antibodies seem to also correlate with the risk of MS [68]. In an attempt to understand how the humoral response towards EBNA-1 impacts the risk of developing MS, it was shown that the levels of circulating IgG against certain EBNA-1 epitopes, particularly those derived from EBNA-1: 385–420 domain, interact with MS risk gene, the HLA genotype DRB1*15 in amplifying MS risk [69]. These findings point to similarities between how HLA molecules influence response to EBV antigens and how they are involved in inducing autoimmune response [70]. Additionally, the humoral response to EBV antigens, specifically anti-EBNA-1 IgG vary between different forms of MS, namely CIS, relapsing–remitting and progressive MS [71], suggesting that the level of these antibodies is not only predictive of MS onset, but also of disease progression. However, it remains debatable whether the humoral level can correlate with markers of disease progression such as volumes of T2 MRI lesions, reflective of demyelinative disease activity and scores of Expanded Disability Status Scale (EDSS), reflective of the progression of physical disability [71–76]. Despite some of these inconsistencies in the serological link between EBV infection and MS, studies agree on the fact that serum antibody titers to EBNA-1 increase prior to developing MS, and hence predictive of MS. In other words, it seems that EBV acts early in provoking an immune (humoral) response towards promoting the onset of MS [77]. However, it is safe to argue that EBV may be a cofactor contributing with other factors, such as genetic susceptibility and vitamin D levels, to the pathogenesis of MS [78, 79].

5. Cellular immune response to EBV in MS

Forty years ago, it was shown that peripheral blood mononuclear cells (PBMCs) taken from patients with active MS, spontaneously transformed into LCLs in *in vitro*

culture more readily than PBMCs taken from healthy controls or patients with inactive MS [80]. These spontaneously immortalized LCLs were of B-cell origin and expressed EBV antigens, including VCA and EBNAs [80]. So, why do PBMCs from active MS patients transform more readily compared to those from healthy controls? One possible explanation is that the immune response to EBV in MS patients is less effective compared to healthy EBV seropositive individuals. Indeed, data from a number of different studies indicates that the T-cell response to EBV is aberrantly regulated in MS patients and it varies at different stages of the disease [81–83]. $CD8^+$ T cells in the blood of MS patients with inactive disease, have been shown to express the immune inhibitory molecule, programmed death 1 (PD-1), making these cells less efficient in eliminating EBV infected cells [84]. This $CD8^+$ T cell exhaustion is believed to be a common feature in many chronic viral infections [85–87], and could explain the conflicting results in EBV viral load detected in MS patients. Thus, the stage of the disease and the level of T cell exhaustion could account for the higher viral load reported in some studies [88, 89], whilst others showed no statistical difference between MS and controls [89–91]. Further support for an aberrant anti-viral immune response in MS comes from the observations that MS patients appear to be at increased risk of acquiring certain viral infections such as influenza [92, 93].

A more recent study investigated B cell transformation of PBMCs taken from 21 MS patients and 21 healthy controls [94]. In order to minimize the effect of T cell control of EBV, which may vary from person to person, T cell activity in all PBMCs cultures was inhibited using cyclosporine A. Cultures obtained from MS patients resulted in significantly higher frequency of B cell transformation compared to healthy controls [94]. Whether this was due to MS patients having a higher frequency of circulating EBV infected cells, or due to higher frequency of viral lytic replication occurring in MS patients is not clear.

There have also been some attempts to examine differences in the cell-mediated immune response against EBV and its antigens in the blood and cerebrospinal fluid (CSF) of MS patients [95, 96]. However, these investigations have also yielded inconsistent results. Whilst some have reported an increase in frequency of both intrathecal EBV reactive $CD4^+$ and $CD8^+$ T cells in MS [96], others have found that only $CD8^+$ T cells and not $CD4^+$ T cells are increased compared to controls [95]. Moreover, intrathecal $CD4^+$ and $CD8^+$ T cells from MS failed to react to a number of common autoantigens suspected to be targets of immune response in MS [97]. Thus, the identity of the target antigen for the autoreactive T cells remains elusive. A very recent study has reported that intrathecal $CD4^+$ T cells from HLA-DRB3 positive MS patients reacted with GDP-L-fucose synthase, an enzyme frequently expressed in human cells as well as in bacteria commonly present in the gastrointestinal track of MS patients [98]. This tantalizing finding warrants further investigations to determine if gut bacterial GDP-L-fucose synthase is indeed the primary trigger for the activation of autoreactive T-cells that subsequently migrate to the brain and lead to demyelination. It is plausible that EBV could also trigger autoreactive T-cells by molecularly mimicry [99–101]. In this context, certain epitopes of EBNA-1, EBNA-3A and LMP2 have been shown to be targets of $CD8^+$ T cell responses and to cross-react with self-antigens associated with MS pathogenesis [102–104]. However, current evidence fails to clearly explain how cell-mediated immune responses to EBV antigens may lead to MS.

6. Direct demonstration of the presence of EBV in MS brains

Compared to the blood and CSF, access to brain tissues, particularly fresh tissues from MS patients has been difficult and limited. In spite of this, a number of studies

have examined brain tissues to explore the link between EBV and the pathogenesis of MS. Most of these investigations have been conducted on formalin-fixed, paraffin-embedded post-mortem tissues. Arguably, these studies have generated the strongest and most convincing data implicating EBV in the development of MS. Initial attempts aimed at directly demonstrating if EBV was present in MS lesions or not, reported either negative results or did not see any difference in EBV positivity between MS and control tissues [105, 106]. A subsequent study however, reported the presence of EBV in 21/22 MS, but not in non-MS inflammatory neurological conditions [107]. The virus was localized to B cells and plasma cells, most notably in the meninges and perivascular infiltrates of active lesions. Additionally, infected cells were found to express a number of viral antigens, latent and lytic [107], making them a potential target of $CD8^+$ T cells and triggering an inflammatory environment in the CNS [82]. Although these findings were confirmed by some subsequent studies [108, 109], others reported absence of EBV infection in the MS brain [110–112]. It was argued that the discrepancies in the findings would be due to many different variables, including differences in the tissue samples examined, variation in tissue preservation and processing, type of fixatives and length of fixation, and the sensitivity and specificity of methods used for EBV detection [113]. Moreover, owing to the great heterogeneity of the brain, the molecular and cellular environment of one region does not necessarily represent another adjacent region, even in the same tissue block [113, 114]. Thus, the absence of EBV in one region of the brain, cannot be interpreted to mean that the virus is absent from all parts of the brain. Keeping some of these variables in mind, we recently conducted an extensive study examining the potential involvement of EBV in MS pathogenesis [115]. We analyzed over 1000 samples from MS cases and non-MS controls using our highly sensitive EBER-*in situ* hybridization, PCR, and immunohistochemistry methodologies [115]. Our findings indicated that EBV was present in most (90%) cases of MS and the virus could be detected in multiple tissue samples from each case. Surprisingly, we found EBV not only in B-cells, but also in astrocytes and some microglial cells. Significantly, the virus was transcriptionally active in these cells and expressed EBNA-1, and to a lesser extent the early lytic cycle protein BZLF1. Taken together, these findings support a role for EBV in the pathogenesis of MS.

7. Proposed model of EBV involvement in MS pathology

The data demonstrating the presence of EBV directly in the brain of MS cases is fairly robust and convincing evidence in support of a role for EBV in the pathogenesis of MS. However, the presence of the virus in the brain cannot be simply interpreted to imply causality. Although it is possible that EBV infection could be a consequence of MS pathology, the observation that EBV seronegative individuals have an almost zero risk of developing MS is strong and compelling evidence supporting a role for EBV in initiating MS. Ironically, although it is believed that T-cells orchestrate and lead the pathogenesis of MS, treatment strategies that have been shown to be most effective in controlling disease activity, involve depleting B-cells [22, 116]. Moreover, depleting memory B-cells, the very cells that harbor EBV, appears to be the most effective [117]. How can these apparently contradictory findings be reconciled? We propose that EBV infected memory B-cells act as antigen presenting cells (APC), resulting in the activation of helper T-cells, which in individuals carrying certain HLA haplotypes, activate autoreactive B and T-cells targeting antigens expressed on oligodendrocytes [102, 118]. In this model (**Figure 1**), disturbances in the integrity of the blood brain barrier (BBB) allows EBV carrying memory B-cells to cross into the CNS, triggering a cascade of events including, attraction of autoreactive B and T-cells, triggering pro-inflammatory

cytokines and microglial activation [118–120]. While most of the EBV infected B-cells infiltrating into the brain remain latently infected, a small percentage are triggered to undergo lytic replication [121, 122, 107], which could explain how CNS resident astrocytes and microglial cells get infected [115]. Infection of astrocytes can be reconciled by the fact that, like B-cells, they also express CD21, the receptor for EBV [123]. Astrocytes are the most abundant cells in the CNS, constituting around 30% of the total cells. They play an important role in a number of homeostatic and neuroinflammatory processes within the CNS, including axon guidance, synaptic transmission and controlling BBB [124, 125]. An accumulating body of data now indicates that activated astrocytes also play a central role in neurodegenerative diseases such as MS [124–126]. Since astrocytes interact with blood vessels to form the BBB, any functional impact on these cells could also increase BBB permeability and exacerbate infiltration of peripheral immune cells into the CNS [120, 125, 127]. This could explain the characteristic perivascular cuffing and presence of inflammatory aggregates resembling germinal center (GC)-like structures commonly observed in the CNS in viral infections [22, 128]. Although the precise role of these tertiary lymphoid aggregates remains unknown, it is likely that they play a key role

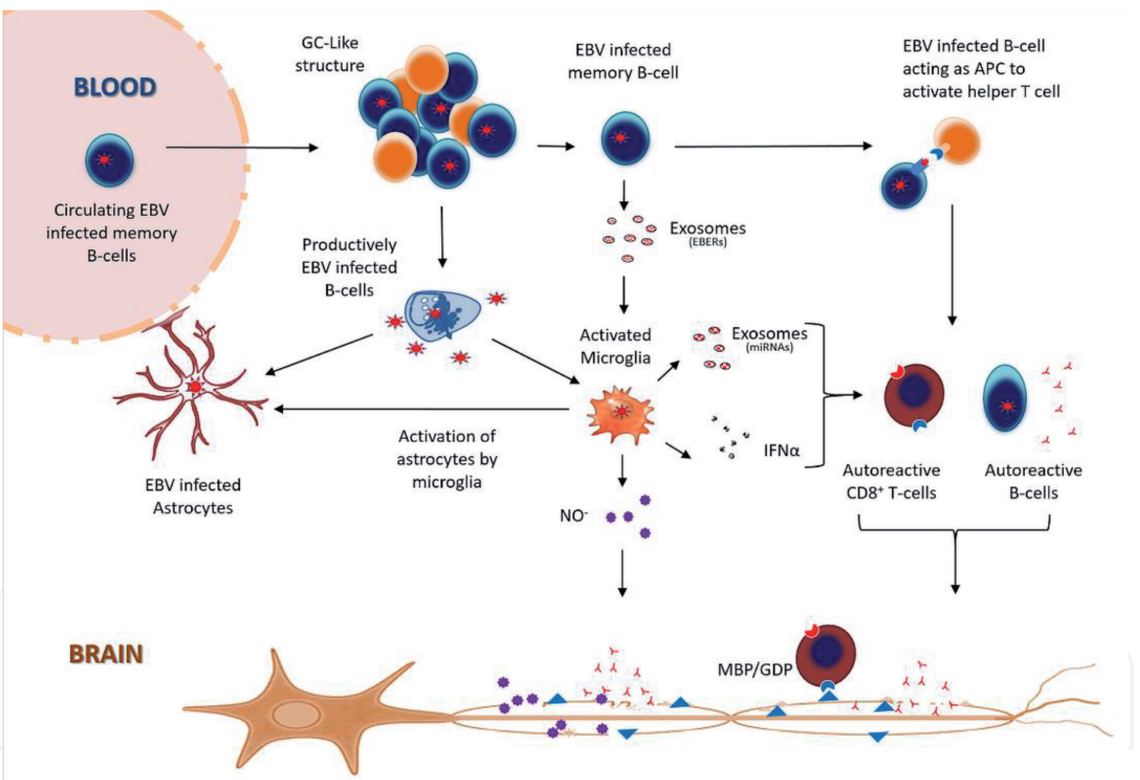

Figure 1.
Model for EBV involvement in MS pathology. The pathogenesis of MS is no doubt very complex. This is a simplified outline of a potential model to explain some of the experimental findings linking EBV to MS. EBV persists in memory B-cells in peripheral circulation [39, 40] and in healthy seropositive individuals, they are tightly regulated by the immune system. In individuals genetically predisposed to MS, these cells cross the BBB and enter the CNS where they trigger an inflammatory response leading to the formation of GC-like structures [128, 129]. Most of the infected cells remain latently infected with limited viral gene expression [107, 108]. These infected cells could function as APC for the activation of helper T-cells [118] which in individuals carrying certain HLA haplotypes [89, 132], leads to the activation of autoreactive B and T-cells that recognize both EBV and self-antigens [99, 101, 118]. A small proportion of EBV infected memory B-cells, upon differentiation into plasma cells, initiate EBV replicative cycle [121, 122]. The new virions produced, infect other susceptible cells, including astrocytes and microglia [115, 123]. Microglia and astrocytes are two main types of cells typically providing a protective role against viral infection. In their activated form, they release various pro-inflammatory cytokines and immune mediators that activate the immune system to resolve the infection [125, 133]. In MS, these chronically activated cells switch from being neuroprotective to neurotoxic [133, 134]. Additionally, proinflammatory microglia can also induce activation of astrocytes, which can impact not only the BBB but also contribute to neurotoxicity [125, 126]. The combined effects of these multiple events result in MS pathology.

in the immune response to CNS injury [129]. In contrast to previously held views, studies now indicate that B-cell differentiation and clonal expansion typically known to occur in secondary lymphoid organs, can also occur in the CNS [130]. This finding also provides an explanation for the source of oligoclonal immunoglobulin bands present in the CSF of most patients with MS. In MS, these GC-like aggregates, triggered by EBV infection of the brain, could be responsible for recruiting, activating and sustaining B and T-cells [119, 118] that inadvertently react to auto-antigens, such as myelin basic protein (MBP) and GDP-L-fucose synthase, expressed on oligodendrocytes (**Figure 1**) [98, 99, 101]. Moreover, cellular and viral components such miRNAs and EBERs, secreted in exosomes could also promote inflammatory and pathological changes that contribute to CNS injury in MS [108, 131].

8. Conclusion

The pathogenesis of MS appears to be a complex process, where both genetic and environmental risk factors interplay to promote the development of the disease. The evidence implicating EBV as a central player in MS development is substantial. For some critics, these pieces of evidence are still not sufficient to charge EBV as the mastermind behind the pathogenesis of MS. A very recent study by Pender and colleagues goes some way to proving the etiological association [135]. The study demonstrated that treating MS patients with autologous EBV-specific T cell therapy can improve symptoms and quality of life in most patients [135]. The only absolute and unequivocal proof that EBV is central to the development of MS, is to prevent EBV infection in the first place by vaccination and then see if the incidence of MS declines. Although a number of vaccine candidates have been tested, none have yet been approved for clinical use [136].

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Conflict of interest

The authors have no conflict of interest.

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