MULTIPLE SCLEROSIS GOES VIRAL: THE IMPACT OF VIRAL INFECTIONS ON THE DEVELOPMENT OF MULTIPLE SCLEROSIS

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Abstract

Review

Multiple Sclerosis (MS) is an autoimmune disease of the central nervous system that has fascinated and bewildered scientists for decades. Patients suffering from MS have an impaired immune tolerance resulting in the emergence of autoreactive immune cells, which infiltrate the brain and spinal cord and attack the myelin sheath of nerves. While the prevalence pattern indicates a genetic component to the development of MS, environmental influences have been identified as crucial players as well, including certain viral infections. Proposed viruses include Epstein-Barr virus, human cytomegalovirus, and endogenous retroviruses, amidst others. The interplay of viral infections and MS development is complicated, and many questions remain unanswered, most notably how viruses exactly increase MS susceptibility. Elucidating these mechanisms could provide valuable insights into immune regulation processes and might be transferable to other immune diseases. Furthermore, a better understanding of the disease aetiology could substantially improve treatments, which are unsatisfying as of now. Thus, research efforts in this exciting field could open up new possibilities for treatments and, hence, in the long term, significantly increase the quality of life of MS patients. This article aims to briefly outline the role of the three aforementioned viruses in MS development and highlight the therapeutical potential of better understanding the connection between viral infections and MS risk.

KEYWORDS: Autoimmune disease, Environmental risk factor, Epstein-Barr virus, Human cytomegalovirus, Endogenous retroviruses

For a long time, autoimmune processes were reckoned to be impossible and long after their introduction in the mid 20th century by Paul Ehrlich, the concept remained highly controversial [1, 2]. Nonetheless, with time, more and more diseases were shown to have autoimmune processes underlying, making autoimmune conditions an important and relatively common family of diseases [3]. One of these diseases is Multiple Sclerosis (MS), an autoimmune condition manifesting in the central nervous system (CNS) with an intriguing prevalence pattern [4]. While MS is rather common in high-income countries (140 and 108 cases per 100,000 individuals for North America and Europe, respectively), it occurs to a much lesser extent in regions like East-Asia and Sub-Saharan Africa with approximately two cases per 100 000 individuals [4]. Several viral infections have been proposed to act as environmental factors, including Epstein-Barr virus (EBV), human cytomegalovirus (CMV), and members of the human endogenous retrovirus family W (HERV-W) [5-7]. However, no concrete conclusion to the debate has been obtained yet. Thus, this review aims to give a broad overview of the disease and the viruses in question, before outlining the current state of knowledge about the impact of viral infections in MS development and highlighting the translation potential of these findings.

Clinical description of the disease

MS is a chronic disease, characterised by inflammatory processes and demyelination events within the CNS, which describes the destruction of the myelin layer that normally isolates nerves from its surroundings [5]. Additionally, varying degrees of damage to neurons and their axons have been described in MS [5]. Symptoms of the disease vary depending on the location of the lesions in the brain and can include decreased control of movement and bladder function as well as reduced cognitive abilities [5]. Two different types of MS can be distinguished when it comes to disease progression [8]. One form is characterised by the appearance of timely restricted symptoms, so-called "relapses", which then vanishes again, giving this form of MS the name "relapsing-remitting MS" [8]. Over time, this form can transform into a secondary progressive state, which is characterised by the continuous worsening of symptoms [8]. However, in 10% of cases, the patient's health status slowly deteriorates from the inception, which is titled primary progressive MS [8].

Life expectancy seems to be similar between the general population and MS patients under 40 (hazard ratio (HR) referring to the likelihood that an individual meets the event, i.e. dies, of 0.63 (95% confidence interval (CI) 0.23–1.70)) [9]. The HR is slightly increased in patients aged 40-59 compared to individuals without MS (HR of 1.68 (95% CI 1.05–2.69)) [9]. Strikingly, the oldest patients (60 years of age and over) showed an HR of 11.37 (95% CI 8.12–15.93), compared to the overall population [9]. These statistics lead us to conclude a directly proportionate rate of mortality with age. Also, the overall HR was increased in the MS population, compared to individuals without MS (HR 3.51, 95% CI 2.63–4.69), which is backed up by previous studies [9-12]. While primary progressive MS was significantly associated with a decrease in life span (risk ratio 1.99; 95% CI 1.52–2.59), the mean age of patients at death was similar between primary progressive MS and relapsing-remitting MS (*p*-value 0.155) [10]. As of now, there is no curative treatment available for MS as the current approaches only slow down the disease progression but do not achieve to halt it completely [8].

Pathogenesis of MS

The pathogenesis of MS is complicated and not fully elucidated yet. As is the case for any autoimmune disease, it is hypothesised that a defective immune tolerance causes MS [13]. Under normal conditions, autoreactive

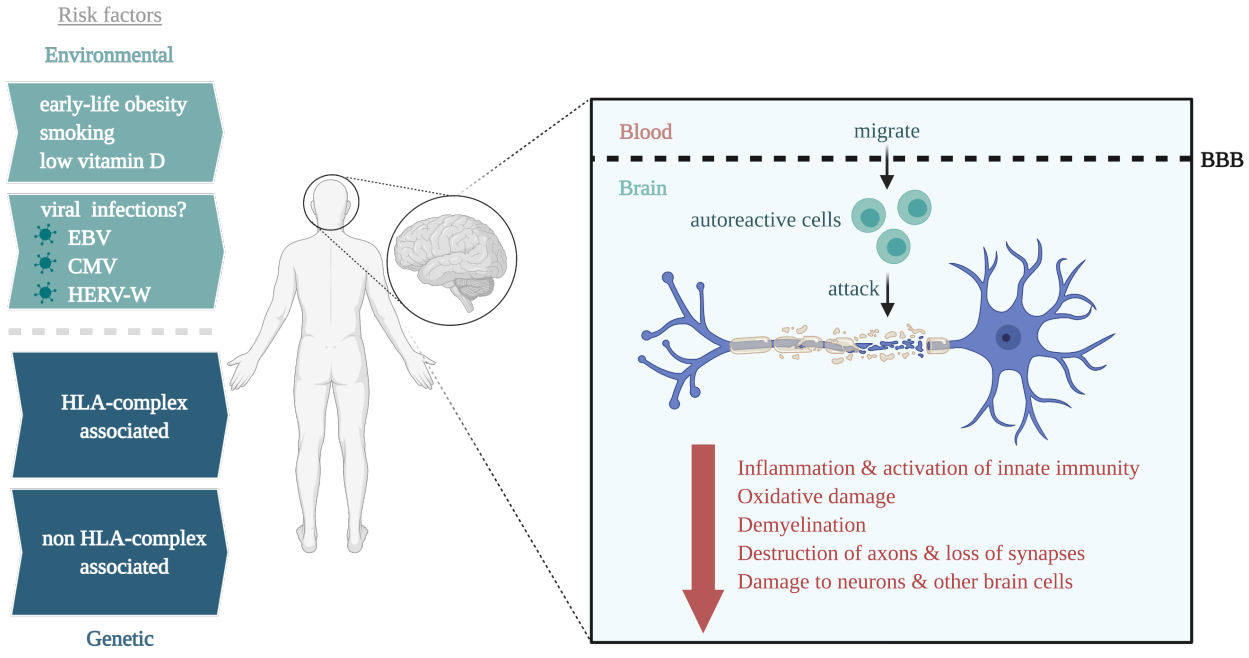

Figure 1: Proposed pathogenesis of multiple sclerosis

MS arises due to a complex interplay of genetic and environmental risk factors. Genetic risk factors include human leukocyte antigen (HLA) complex-associated and non-HLA complex-associated alleles. Regarding environmental risk factors, several are thought to impact MS risk, including early-life obesity, smoking, and low serum vitamin D levels. Furthermore, also certain viral infections might be facilitating MS development, including Epstein-Barr virus (EBV), human cytomegalovirus (CMV) and, members of the human endogenous retrovirus family W (HERV-W). These risk factors promote the emergence of autoreactive cells that migrate into the central nervous system (CNS) via the blood-brain barrier (BBB). There they attack the myelin covering of neurons. This process results in demyelination, destructions of axons, loss of synapses, and damage to neurons and other brain cells, as well as inflammation and activation of the innate immune system and oxidative damage. Created with BioRender.com.

immune cells of the adaptive immune system are inactivated or removed by apoptosis. However, in MS, they are thought to persist and become activated [13]. These cells then enter the CNS and damage the myelin isolation of neurons, resulting in demyelination, as well as the loss of synapses, axonal injury, and damage to neurons and other brain cells [13]. These localised spots of tissue damage, called "demyelinated plaques", show up as lesions on MRI scans and are associated with the further breakdown of the blood-brain barrier [13]. Due to the increase in barrier permeability, there is enhanced leukocyte infiltration into the CNS [13]. Within lesions and the surrounding tissue, several immune cell types are present, including B- and T-lymphocytes, monocyte-derived macrophages, natural killer cells, neutrophils, and microglia [14-16]. The damage is only insufficiently repaired and gets exacerbated by processes involving the activation of innate immunity in the CNS and oxidative damage, amongst others [13]. Combined with the exhaustion of the compensatory mechanisms of the CNS over time, these processes then lead to further decline of neurological functions [13].

In earlier times, MS was thought to be primarily a T-cell-mediated disease and there is ample data to substantiate this [17, 18]. However, several clinical trials were able to show that the use of B-cell depleting antibodies decreased disease activity, also indicating a role for B-cells in disease pathogenesis [19, 20]. The role of B-cells seems primarily to be centred around antigen presentation and the production of proinflammatory cyto- and chemokines as opposed to antibody production. This conclusion is based on studies showing a fast improvement of symptoms upon B-cell depleting therapy and others which determined the absence of autoantibodies [21].

Risk factors

So far, no single genetic determinant of MS has been reported [5]. A comparison of large population-based twin studies support a genetic contribution to MS risk; however, the extent is still subject to debate [22]. Instead of a sole genetic source, MS rather seems to arise due to a complex interplay between genetic risk factors and environmental factors [8]. Genetic risk factors are mainly found in loci associated with the human leukocyte antigen complex and thereby impact the presentation of antigens to T-lymphocytes [8]. Nevertheless, other gene variants have been implicated as well [8].

Currently, it is theorised that MS occurs in individuals who are susceptible to the disease due to their genetic background and additionally experience a combination of environmental factors [5]. The combination of environmental circumstances needed to initiate MS in a patient seems to be highly variable, differing both in the composition of factors as well as their individual contribution to MS progression [21]. The proposed environmental factors increasing MS risk are numerous and include smoking, obesity in early life, and low vitamin D levels [8]. Notably, also viral infections are discussed in their implication in augmenting MS risk, and some of the potential viral players are discussed below in an attempt to give an overview of the proposed interaction models.

Viral infections as environmental risk factors

Viral infections as initiators of autoimmune diseases have been extensively reviewed, with the conclusion that some viruses can definitely give rise to autoimmunity [23, 24]. However, for MS, the situation remains less clear [8]. There are several viruses discussed in connection to MS development, with some viruses remaining more controversial than others [8]. This review will focus on three examples, namely EBV, human CMV, and HERV-W (Figure 1) [5-7].

Of note, this is an active, dynamic field of research and therefore, new theories about how viral infections act in MS pathogenesis arise and are overturned almost on a daily basis [25]. The most substantiated hypotheses are outlined below, although the list is by no means exhaustive [25]. Firstly, there is molecular mimicry, which describes the induction of an immune response against a viral antigen, that is similar to a self-antigen, thereby potentially promoting an autoimmune response [25]. This can also result in epitope spreading, a process where the body starts fighting viral antigens, but due to the damage following the immune response, also self-antigens are released [25]. The immune system then falsely recognises them as viral antigens and induces an immune response, resulting in autoimmunity [25]. Another possible theory is titled "bystander activation" and describes a situation where viral products activate formerly inactive dendritic cells presenting self-antigens [25]. These then stimulate the emergence of autoreactive T-cells, thereby promoting autoimmunity [25]. However, in recent years, the bystander activation theory has been increasingly regarded as unlikely to be the major mechanism [25]. Lastly, it might be the case that two viral infections are needed to induce MS development, one acting as a priming factor and the other virus finally inducing MS years later [25]. This, however, has only so far been described in animal models of MS [25].

Research in this field is difficult, and often, the results are inconclusive [26]. One of the biggest hurdles is the small cohorts of eligible participants within a study [26]. This reduces the power of an analysis to pick up a certain effect and can potentially result in a lack of significance [26]. Furthermore, often important information on health aspects of the individual are not available for all participants, which impedes the analysis [26]. Finally, it needs to be acknowledged that correlation does not necessarily entail causation [6]. Thus, epidemiological evidence can never establish a causal link between two aspects and needs to be backed up with experimental data in MS models [6].

Epstein-Barr virus

EBV is a member of the family of herpesviruses and ubiquitously found in humans [5]. Following an EBV infection, EBV-specific antibodies can be found in individuals, who are then described as EBV seropositive [5]. Symptoms of EBV-induced disease differ depending on the age of the infected person [5]. While EBV infections in prepubertal individuals are asymptomatic, adolescents and adults can develop infectious mononucleosis (IM) [5]. IM is the clinical manifestation of acute EBV infections and characterised by symptoms like fever, inflammation of the throat, and enlargement of the lymph nodes [5, 27].

EBV has been associated with the occurrence of MS following a number of epidemiological studies that investigated the correlation between EBV seropositivity or a history of IM, and MS in individuals. Firstly, in a serological study from 2011, all included MS patients were either initially seropositive for EBV or turned seropositive before the onset of MS [28]. Secondly, a meta-analysis of 18 studies highlighted that the risk of developing MS is two- to three-fold higher for individuals with a recorded history of IM than the risk for individuals that never experienced IM [29]. Conversely, seronegativity seems to be negatively associated with MS [30]. A meta-analysis calculated the MS risk of a member of the EBV seronegative cohort at 0.06, which is decidedly lower than average (95% CI 0.03-0.13) [30]. Lastly, this correlation is backed up by serological data, which correlated the risk of MS with EBV-specific antibodies [28]. In the largest study, conducted by Munger *et al.* in 2011, a striking correlation was found between the levels of immunoglobulin G antibodies targeting the Epstein-Barr nuclear antigen (EBNA) complex and MS risk (p-value $2.1E^{-13}$) [28]. Furthermore, similar trends also appeared concerning other EBV-specific antibodies and the risk of developing MS (p-values $5.7E^{-9}$ for EBNA1, $9E^{-4}$ for EBNA2, and $5.7E^{-7}$ for the viral capsid antigen) [28].

The exact mechanism of how EBV infection influences the pathogenesis of MS is not fully elucidated yet; however, numerous theories are currently being investigated. Interestingly, cross-reactivity of EBNA1 with human heterogeneous nuclear ribonucleoprotein L, a known autoantigen in MS, has been described [31]. This strengthens the idea of molecular mimicry. Furthermore, also EBV-specific mechanisms are debated, such as the leakage of EBV-infected B-cells into the CNS, where they induce a pro-inflammatory environment [5, 25].

Notably, rather than exposure to the virus itself (i.e. EBV seropositivity), the clinical manifestation of the EBV-infection in the form of IM seems to determine the risk of developing MS [30]. This phenomenon can be explained by the hygiene hypothesis [30]. It states that early exposure to infections can aid the formation of immunoregulatory mechanisms, which then convey protection against pathogenicity of autoreactive cells [32, 33]. The hygiene hypothesis is substantiated by evidence derived from other prevalent pathogens in the context of MS, like *Helicobacter pylori* [34]. Due to MS being a multifactorial disease, it is, up to this day, difficult to determine causality between EBV and MS, despite the extensive evidence [8]. More research will be necessary to elucidate mechanisms by which EBV could induce MS.

Human cytomegalovirus

Human CMV is a member of the family of herpesviruses (just like EBV) and ubiquitously present in adults [6]. The role of CMV in MS development is highly controversial and both evidence for a protective as well as for a harmful role has been acquired [6]. In a recent transethnic case-control study investigating CMV seropositivity in correlation with MS risk, CMV was shown to have a protective effect [35]. However, this effect was only found in Hispanic individuals, as opposed to black or white study participants [36]. This raises the possibility that the protective effect is actually due to a yet to be determined confounder, instead of CMV [36]. Additionally, a meta-analysis of previously published studies performed by Pakpoor *et al.* in 2013 did not find conclusive evidence in favour of an association between CMV infections and decreased MS risk [36].

Nevertheless, one study described a reduced likelihood for pediatric-onset MS, which is characterised by an emergence of the disease during childhood, in the case of CMV seropositivity [37]. This was later broadened to all types of MS when, in 2013, a meta-analysis claimed CMV infection to be associated with a lower MS risk in general [26]. However, both studies are retrospective, which leaves room for doubts [26]. For instance, during the long periods between initial serological tests and the following classification of MS progression, initially seronegative patients can become infected with the virus [26]. This could potentially skew the results [26]. Additionally, the statistics of retrospective meta-analysis can be misleading [26]. In the meta-analysis performed by Sundquist *et al.* in 2013, for example, eleven studies were included, of which only two initially showed a significant association between CMV seropositivity and MS development [26]. Nevertheless, the overall meta-analysis also concluded that CMV seropositivity and MS risk are significantly associated [26].

To conclude, the effect of CMV infection on the risk of developing MS remains highly debated, and no conclusive evidence has been brought forward to explain the complex interplay. In an attempt to explain the outlined inconsistencies, the possibility has been raised that CMV may have opposite effects on MS development and the course of the disease and may have stronger detrimental effects at later stages [33].

Endogenous retroviruses

Endogenous retroviruses (ERVs) describe repetitive genomic sequences which are thought to derive from retroviruses infecting germline cells and integrating into their host cell genome [38]. In humans, they are no longer active as infectious viruses, although both viral RNA and proteins are expressed. Furthermore, interactions between the regulatory elements within the viral genome and cellular transcription factors have been identified [38]. This raises the possibility that the consistent presence of viral products impacts cellular processes, including (auto-)immunity [38].

The association of MS and human ERVs (HERVs) is highly controversial, albeit several systematic reviews and meta-analysis recently illustrated that, compared to healthy individuals, MS patients over-express RNA from a specific HERV family, namely the HERV-W family [7]. Other ERV families are also discussed in the context of MS; however, the gathered evidence is less strong [7]. HERV-W is constitutively expressed in the CNS [39]. The proposed mechanism of how HERV-W members facilitate the development of MS centres around the expressed envelope proteins of these endogenous retroviruses [40]. These proteins can activate Toll-like receptor 4 *in vitro*, which promotes the secretion of several proinflammatory cytokines [40]. HERV-W proteins further were shown to lead to the development of neuroinflammation, as well as myelin and oligodendrocyte damage *in vivo* [40]. In fact, the envelope protein of HERV-W is considered as a superantigen, which, after administration to mice, induces systemic inflammation [40]. Of note, systemic inflammation has also been observed in MS in the form of peripheral T-cell activation [40]. Expression of the HERV-W envelope protein has been described in microglial cells and macrophages in MS brains close to MS lesions and might there drive neuroinflammation [40]. However, proteins of other HERV families were shown to act immunosuppressive by inducing immunomodulatory macrophages, which makes the picture more facetted [41]. Thus, a consensus of the impact of HERV products on MS risk is yet to be reached, and more research will be necessary to elucidate the exact effect HERV family members have on MS development.

Translational potential

While MS is, in most cases, not directly fatal, it does have a substantial impact on the quality of life and can reduce life expectancy [9, 42]. Furthermore, biomarkers to recognise at-risk individuals for MS are still lacking [25]. In addition, albeit there are treatments available, they do not achieve satisfying results for all types of MS progressions [8]. Therefore, there is still an unmet clinical need for better treatments to actually halt disease progression. A better understanding of the interaction between viral infections and MS could enable us to discover biomarkers to (i) identify individuals with a higher MS risk and (ii) predict disease progression in patients diagnosed with MS, while also aiding in the development of new therapeutic approaches [25]. As of 2017, several treatments primarily targeting viruses underwent trials of varying clinical phases in the context of MS [43]. Most notably, the antiviral compound acyclovir and its prodrug valacyclovir targeting herpesviruses took part in three phase III trials in the last decades [43]. Upon subgrouping the patients according to disease activity, treatment resulted in a 34% reduction in relapse rate in patients with high disease activity [44]. Another study indicated a decrease in baseline disease activity following anti-herpes virus therapy in comparison to a placebo-treated group due to a decreased number of active CNS lesions in MS patients undergoing treatment [45]. Thus, while the primary ends of the trials were not met, the results look promising nonetheless and give hope for the use of antiviral drugs in treating MS [43].

Conclusion

In conclusion, MS remains a medical challenge due to the elusive disease pathogenesis, lack of prognostic biomarkers and inadequate treatment options. The complex interplay between genetic and environmental risk factors further increases the difficulties in preventing and treating MS. Understanding how viral infections interact with the MS risk in genetically susceptible individuals will be pivotal in understanding the molecular mechanisms behind the disease and finding better treatment approaches. Furthermore, findings in this field might offer valuable insights for other autoimmune diseases as well. Antiviral treatments hold the potential to meet a current gap in medical care and improve the quality of life for MS patients.

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