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Could Multiple Sclerosis Develop due to Epstein Barr Virus Infections Causing a Time-Delayed Transcriptional-Activation of Human Endogenous Retroviruses?

Jacob Z Dalgaard*

The University of Warwick, Coventry, England, UK

Abstract

The underlying cause of multiple sclerosis (MS) is not fully understood. However, it is known that Epstein Barr virus (EBV) infections pre-date the development of the disease. Here I explore whether the underlying cause of Multiple Sclerosis can be explained by an inappropriate intra-cellular transcriptional response to the integration of the EBV in the genome of neural cells. Such a re-programming is proposed to lead to the transcriptional activation of other dormant viruses, human endogenous retroviruses (HERVs), followed by the "auto-immune" response and inflammation observed in the brain of MS patients?

Keywords: Multiple sclerosis; Epstein barr virus; HERVs; Human endogenous retroviruses; Vitamin D; Transcription regulation; Epigenetics

Multiple sclerosis (MS) is a chronic inflammatory disease leading to demyelination (loss of oligodendrocytes) and axon injury within the central nervous system. Both genetic and environmental factors have been attributed to MS risk. The major risk factor for MS is EBV [1-12]. EBV belongs to the herpes virus family, known to infect the central nervous system (CNS). Approximately 90% of the population carries antibodies to EBV; most people are exposed to the virus in childhood-where the disease pattern is asymptomatic, while virus infections in teenage years or later in life, leads to a more severe disease referred to as mononucleosis. People that have not been exposed to the virus have a very low risk of developing MS; however, if they are exposed to EBV during childhood they will have a significant risk of developing the disease later in life (less than a 0.2% chance). This risk increases further 2-3 fold if the EBV infection leads to mononucleosis [13]. Under normal EBV infections, the virus will at some point migrate through the peripheral neural axons to the CNS, enter the cells nucleus and integrate itself into the genome. Here the virus enters a latent stage with very low levels of viral gene-expression. This silenced stage is dependent on host factors.

Here I propose that: A) due to the maintenance of this latent/dormant EBV stage is defective in MS patients, or B) due to the low-level expression of the latent virus; the EBV causes changes in the transcription programme of the neural host cell, leading to an activation of other dormant viruses (HERVs; see below). In this model, MS is the direct result of the immunological and inflammatory response to this "inappropriate" expression of viral proteins and genomes in the CNS.

Herpes viruses are not the only family of viruses that integrate themselves into the host genome. Retroviruses are also able to enter an integrated latent stage and have earlier been proposed to be involved in MS [14-16]. Indeed, towards 8% of our genomic DNA consists of DNA of retroviral origin [17]. The majority of such DNA is LTR (Long Terminal Repeat) sequences lacking open reading frames. However, some elements (Human Endogenous Retroviruses; HERV) possess functional open reading frames. There are several clinical observations that have been proposed to support a role for HERVs in MS:

I) MS patients are characterized by the presences of immunoglobulins in the cerebrospinal fluid. In general, viral CNS infections in non-MS patients can lead to the appearance of antibodies in the cerebrospinal fluid specifically targeted towards the pathogen, however, in MS patients the cerebrospinal fluid antibodies are diverse, recognizing several viral antigens including EBV and HERVs [18].

II) It has been shown that most, but not all, MS patient's lymphocytes express reverse-transcriptase positive retroviral-like HERV particles [19-21].

III) The adaptive immune response to certain HERVs is elevated in most MS patients, especially when MS is active [22-24].

IV) HERV antigens exhibit elevated expression levels in peripheral mono-nuclear blood cells from MS patients [25-27].

V) In a Sardinian cohort of MS patients a correlation between levels of retroviral related RNAs in the cerebrospinal fluid and disease prognosis has been established [28].

VI) A study looking at transcriptional levels found that transcription levels of HERVs (HERV-H, HERV-K and HERV-W) are higher in MS CSN cells [29].

How would it be possible that an initial EBV infection, low-level latent EBV expression or defective silencing of integrated EBVs, subsequently could lead to a time-delayed expression of HERVs? Although the mechanism is not known, such an effect has already been described in another system: A very interesting set of experiments, looking at cocaine addiction in rats, showed that approximately 20% of the animals having had a single exposure to the drug developed changes in the CNS gene expression and DNA methylation profiles

***Corresponding author:** Jacob Z Dalgaard, The University of Warwick, Coventry, Farmer Ward Road Kenilworth, Warwickshire CV82DJ, United Kingdom, Tel: 44(0)1926851170/44(0)7939692966; E-mail: jzeuthendalgaard@gmail.com

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[30]. Importantly these changes did not occur at the time of cocaine exposure, but in a delayed manner during extended periods after the initial exposure. The rats, where the changes occurred, were the ones that subsequently became addicted when they were re-exposed to cocaine. Similarly, in MS patients, EBV infection and virus integration in the neurons could, in a similar sub-population, lead to time delayed changes in the gene-expression program in the CNS, including to the reactivation of HERVs. Such a re-activation would then provoke an "auto"-immune response, as they potentially would not have been expressed during B-cell and T-cell maturation and clonal elimination.

How would this a model fit the genetic linkage studies? Interestingly, while Genome Wide Association Studies have identified a large number (more than 100) of single nucleotide polymorphisms (SNPs) that show linkage dis-equibrilium with regards to MS risk [31-38]. However, each SNP linked marker only slightly increases the risk of developing MS, adding up to a 54% genetic cause of the disease. Importantly, the SNP linked to the MHC allele HLA-DR2 (DRB1*1501)/DQ6 (DQB1*0602) shows the strongest genetic association with MS risk, increasing the odds 3.08 fold [31,39,40]. MHC molecules are involved in displaying peptides, generated within the cell, to the immune-system, and this MHC mediated display acted to establish an immune-response to viral infections.

Another SNP that has been linked to increased MS risk is associated with NF-kβ, a factor that plays a central role in the inflammatory response [37,41].

Similarly, as expected, other SNPs associated with minor increased MS risks, are in the vicinity of other gene involved in the immune and inflammatory responses [32,35,41-43].

However, in support of the proposed model, a subsequent study has established that there is a significant over-representation, among the MS-risk associated SNPs, of SNPs that are in the vicinity of HERVs [44]. This observation adds direct support for the importance of these elements in the MS disease development.

An additional observation that supports the proposed model for the establishment MS is the observation that retroviral drugs inhibit the MS development; HIV-positive patients that receive anti-retroviral drug treatment show a decreased risk of developing MS [45,46]. Indeed, one HIV-positive patient with MS recovered completely when she was put on anti-retroviral drugs [47] and it was indeed proposed in this study that it could be due to the drugs effect on HERVs.

Finally, the in the public most well-known risk factor for MS is the patients' geographical latitude in regards to residence [48,49]. This effect on MS disease risk has been proposed to be due to different vitamin D levels in patients due to differences in sun exposure [50]. In support of this, recent studies have established linkage between four alleles significantly affecting (decreased) levels of the vitamin D precursor 25-hydroxy vitamin D, and MS risk. However, the increased risk was only two-fold greater [51]. Vitamin D deficiency has been shown to lead to excessive B-cell response in MS patients [52]. Alternatively, both vitamin D and the geographical latitude of the patients' residence could also have a more direct effect on the establishment of the disease through an effect on the transcriptional programme in neurons. In this context, it is noteworthy that another patient, Dr. Wahls, has shown an astonishing recovery from this otherwise chronic disease, after making significant changes to her diet [53]. Importantly, the diet she is following is very rich in brassica, known to have anti-inflammatory effects, and which are a source of isothiocyanates. These compounds inhibit both histone deacetylase transferases and DNA-methyltransferases [54]. Although histone de-acetylase and DNA-methyltransferases inhibitors could seem counter-intuitive in causing silencing of integrated EBV/HERVs, it is well known that activation of one subset of genes by de-silencing, can lead to repression of another sub-set of genes.

In conclusion, I would like to add that if this model is correct, MS patients should be treated with a combination of drugs; including retrovirals (currently being tested for treatment of MS), anti-inflammatory and immune-suppressing drugs, potentially combined with the brassica rich diet. Importantly, since the MS symptoms only express themselves once inflammation and de-myelination have occurred, any treatment has to be maintained for extended periods of time to allow persistent inactivation of the inflammatory and immunological responses, and for the re-myelination of the neurons by the oligodendrocytes.

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