

Epstein-Barr virus and multiple sclerosis

What is EBV?

The Epstein-Barr virus (EBV) is one of the most common viruses to infect humans. Up to 95% of people across the world have been infected with EBV, which is transmitted through bodily fluids such as saliva. EBV is most often acquired during early childhood or young adulthood. EBV infection can be asymptomatic or can cause infectious mononucleosis, also known as glandular fever. Infectious mononucleosis is more likely to occur when EBV infection occurs in later adolescence or early adulthood.

EBV infects human B cells (a type of white blood cells; lymphocytes) and then becomes latent, meaning it remains in the cells even if its presence is asymptomatic. In this stage the virus limits its activity, which allows it to evade the host's immune surveillance. Thus, once someone has experienced EBV infection (even if they did not have any symptoms), they have infected B cells for life. Periodically, EBV reactivates inside the infected B cell, and people shed EBV in their saliva, which can be shared with others. This is why EBV infection is so common.

EBV as an MS risk factor and potential disease trigger

Does EBV cause MS? Will individuals who have been infected with EBV automatically develop MS?

MS is likely caused by a combination of genetic risk factors and environmental exposures including: EBV, smoking, low vitamin D levels (either due to low ultraviolet (sunlight) exposure or low levels of vitamin D intake in the diet), and childhood or adolescent obesity.

At least 99% of people with MS have been infected with EBV, but over 90% of their community has also been infected. Most people with EBV do not develop MS, meaning EBV on its own is insufficient to cause MS. However, it is exceedingly rare for a person to have MS and not have prior EBV infection. The risk of MS is higher in individuals who have had clinical infectious mononucleosis, suggesting that the severity of EBV infection might play a role in this small subgroup of people with MS.

Evidence for EBV as a risk factor for MS

The most convincing evidence linking EBV and MS risk was a study of 10 million active duty members of the US military, of whom 801 were diagnosed with MS and had banked samples every 2 years from enrolment in the military available for analysis. Only one of the 801 people diagnosed with MS remained EBV negative. Of the 35 MS patients who were EBV negative at their first blood sample, all but one was infected with EBV before the onset of the MS (typically about 5 years prior). Overall, EBV infection led to a 32-fold higher risk of MS compared to age-matched military members who did not acquire EBV infection. There was no difference in infection rates for cytomegalovirus (CMV), which is a virus similar to EBV but not known to relate to MS.

The investigators also studied blood biomarkers associated with brain tissue injury (which occurs in people with MS due to the immune system attacking the brain). One key biomarker, serum neurofilament light chain (sNfL) levels increased only after EBV infection, and only in the EBV positive MS patients. Military members who acquired EBV infection, but did not have MS, did not show the increase in sNfL. The fact that the EBV infection occurred before sNfL levels increased is important. This finding suggests that the brain injury caused by MS (and associated with high sNfL levels) did not happen prior to EBV infection, suggesting that the EBV infection was an important pre-requisite for MS, making it very unlikely that having MS predisposes to EBV infection.

In a separate study of 670 Swedish participants, blood samples from individuals taken over several years were used to compare people who went on to develop MS to those who did not develop MS. The people who went on to develop MS were infected with EBV 15-20 years before their MS diagnosis. The researchers also measured an increase in sNfL levels in the blood 5-10 years before the onset of MS – but after the EBV infection.

To prove that EBV is one key cause of MS, we need more than the very strong evidence linking EBV infection to MS risk. We now need to understand what EBV infection does to the immune system, and how this contributes to the immune attack on the brain, optic nerves, and spinal cord that are the fundamental aspects of MS.

Even if researchers can prove that EBV is necessary for the development of MS, we know that EBV alone is not enough to cause MS because most people infected with EBV do not develop the disease. There are still many unanswered questions. Why do some EBV-infected people develop MS, while others do not? How does EBV interact with other risk factors? It is unclear whether genetic or environmental factors work together with EBV or if these factors act independently to increase overall MS risk.

How could EBV trigger MS?

The mechanism by which EBV could potentially cause or 'trigger' MS is not yet fully understood, and research to investigate this question is still ongoing.

Molecular mimicry – one possible mechanism

When a person is infected with EBV, the immune system responds by producing antibodies and activated immune cells, which help to fight the virus. In some individuals, the immune response to EBV may be abnormal and attack the body's own tissues. A part of EBV called the Epstein-Barr nuclear antigen 1 (EBNA1) resembles a molecule found in the brain known as GlialCAM. Therefore, the antibodies created against the EBNA1 may falsely recognise GlialCAM and thus become autoantibodies (antibodies against the body). Instead of just recognising the virus with the aim to destroy it, the immune system also recognises a part of the brain and mistakenly attacks it. This is called molecular mimicry.

Uncontrolled EBV reactivation

The immune system has built-in safety mechanisms that normally destroy immune cells when they mistakenly attack our own body tissues. However, EBV infects B cells and reprograms them to allow the virus to remain inside the B cell ("latent infection"). When the virus re-activates periodically, several things occur. Not only do the EBV infected B cells multiply, they also might react against tissues that look like the EBV proteins (as mentioned in the molecular

mimicry section). The presence of EBV-infected B cells also stimulates normal immune cells to respond, creating an increasingly active immune system – which could lead to greater immune activity in the brain of a person with MS.

How a person's genetics and the environment may play a role

As mentioned above, while almost everyone is infected with EBV during their lifetime, a small number of people develop MS. This means that there are factors other than EBV that play a role in the cause of MS. Some specific genes, like the ones that create proteins called human leukocyte antigens (HLA), control how our immune system reacts to invaders. Other genes may affect EBV-related proteins. These genes are really important because they influence the process of 'molecular mimicry'. In some individuals with MS, a part of the region which recognises EBV proteins may be altered, reducing the immune system's ability to fight EBV.

It is unclear how EBV interacts with other environmental factors. Tobacco smoking leads to inflammation in the lungs and the lymph nodes in the airway. Smokers also have higher levels of EBV antibodies compared to those who do not smoke, and smoking has been associated with frequent activation of EBV. Obesity increases immune responses in adipose tissue and vitamin D deficiency may impair the immune response to EBV. Thus, tobacco, low vitamin D levels, and obesity may create an environment of heightened inflammation which may contribute to MS. Whether these contributions to MS risk relate to EBV directly is unknown.

Could we prevent MS by vaccinating against EBV?

Vaccines are being developed that might be able to prevent or reduce EBV infection if provided to the population. To learn whether EBV vaccines might prevent or reduce MS, it would be necessary to develop a large EBV vaccine study. This study would require vaccination of the general population and then careful monitoring over 20-40 years to determine whether the rate of MS declines.

If the vaccine effectively eradicates EBV in a large portion of people and EBV is causally linked to MS, we should observe a reduction in the number of individuals diagnosed with MS. However, if the EBV vaccine trials successfully eradicate EBV in a large portion of people, but EBV is not the sole risk factor for developing MS, there may still be a reduction in the number of people who develop MS but not all MS would be prevented.

These studies are challenging, as you would have to vaccinate individuals before EBV infection, which means the studies would need to be in children or adolescents, who were then followed for decades after vaccination. Since most people with EBV do not develop MS, it would need to be a very large study. If individuals at higher MS risk, such as family members of people with MS were selected, the study size might be smaller but since (i) the risk of MS is only 3-5% in children of parents with MS, there would still need to be a very large number of children enrolled; (ii) the genetic contributions to MS risk will be inflated in such a study by virtue of only including familial MS and thus results might not apply to all people with MS.

A Phase 2 clinical trial of an EBV vaccine in 2007 reduced the severity of symptoms of infectious mononucleosis, but did not prevent EBV infection. Technical advances of mRNA vaccines during the global COVID-19 pandemic have led companies like Moderna to start Phase 1 trials against EBV. The Moderna vaccine safety study is predicted to be completed in 2025. If successful, follow-up studies would be required to determine if the vaccine is effective in preventing EBV infection.

Not all researchers agree with the approach of EBV vaccination as prevention. Some have pointed out that vaccinating against EBV in childhood could have the effect of delaying EBV infections to adolescence, if the vaccine did not lead to full EBV immunity. Delaying EBV infection into adolescence or early adulthood, ages when people are more likely to experience infectious mononucleosis, could actually increase MS risk.

EBV as a disease driver

There is growing evidence that EBV may be a likely contributing cause of MS, but its role as an ongoing disease driver is not yet clear. In other words, researchers are studying whether EBV is also the engine which makes the disease continue to run, in addition to starting it. Studies are taking place to understand if active EBV infection is linked to ongoing MS disease activity, but also to understand in which part of the body EBV is active, and how some disease-modifying therapies affect EBV activity.

Two studies have found a correlation in people with MS between the amount of EBV antibodies they have, and the degree of disease activity, brain atrophy (the loss or shrinkage of brain tissue), and lesion activity (new or active areas of inflammation in the brain) they experience.

Treating MS by specifically targeting EBV

If EBV has an important role in driving inflammation in MS, then targeting EBV activity in people infected with EBV might be a treatment strategy

Antiviral therapies are one potential way of targeting EBV in people with MS. The antiviral drug valomaciclovir has been shown to be effective in trials for EBV-mediated infectious mononucleosis. It is an antiviral that penetrates the blood-brain barrier and can therefore access the brain and spinal cord, which is highly relevant if EBV infection in the brain plays a significant role in driving ongoing MS.

There is now an ongoing Phase 2 clinical trial by Atara Biotherapeutics studying a therapy which searches the body specifically for EBV-infected B cells and destroys them. This therapy is being tested in people with primary progressive MS and secondary progressive MS. They expect to report results in October 2023.

It is important to remember that some disease-modifying therapies currently used, such as the anti-CD20 therapies ocrelizumab, ofatumumab, and rituximab, are effective because they seek out specific B cells and destroy them. Some researchers believe that one of the reasons they are so effective is because they kill EBV-infected B cells, thereby reducing this potential disease driver.

These types of studies into how different drugs affect EBV infection and MS disease activity will also lead to greater understanding about the potential role of EBV in driving the disease once it has been triggered.

Concluding summary

There is now compelling evidence linking EBV infection with MS risk. Data showing that EBV infection appears to occur before MS onset, makes it highly probable that EBV may be

necessary—but not sufficient—to cause MS. Whether EBV vaccines hold promise in reducing or preventing MS are exciting areas of discussion and challenging future areas of research.

For people living with MS, another important avenue of research relates to studies of EBV influence on MS disease activity. It is not yet clear whether EBV re-activation might drive some aspects of relapsing immune responses in MS, and whether strategies to modulate EBV activity might also reduce MS disease activity.

Finally, all studies will need to fully appreciate the intricate relationship between EBV and the human immune system. Could there be any unanticipated consequences of reducing EBV infection worldwide, or of modulating EBV behaviour in the human host?

What our members say about EBV

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