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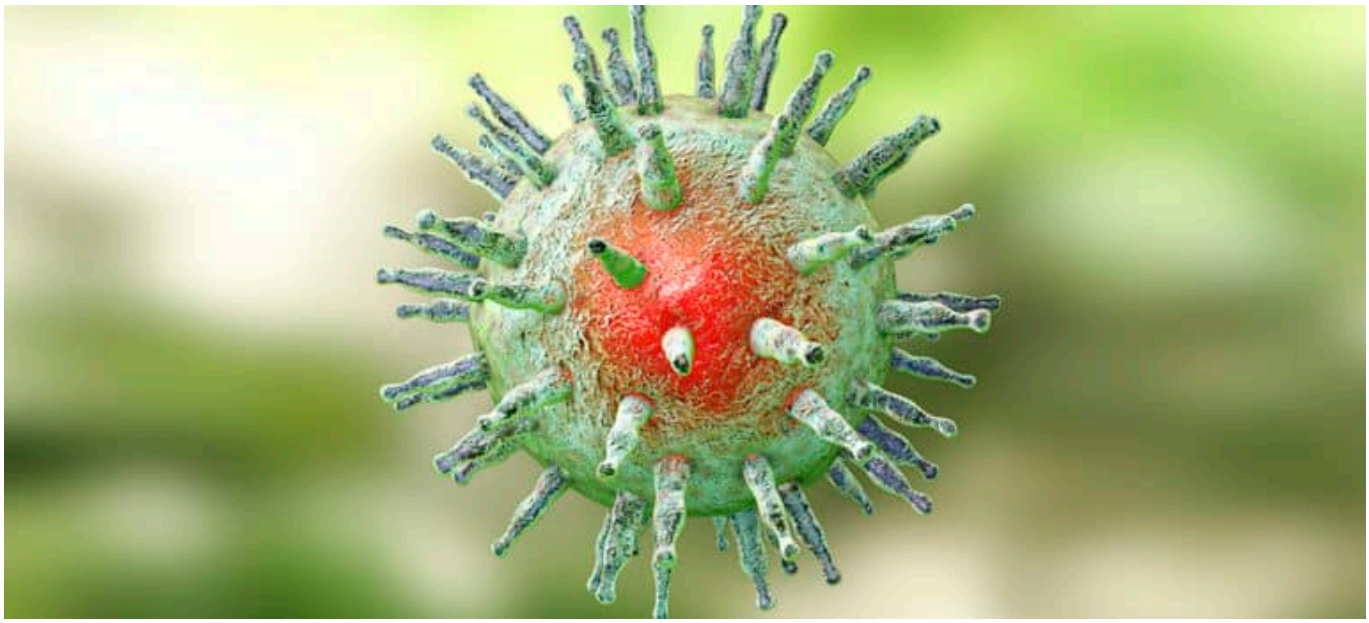


Studies show Epstein-Barr virus as a major risk factor for MS.

by Mary E. King, PhD

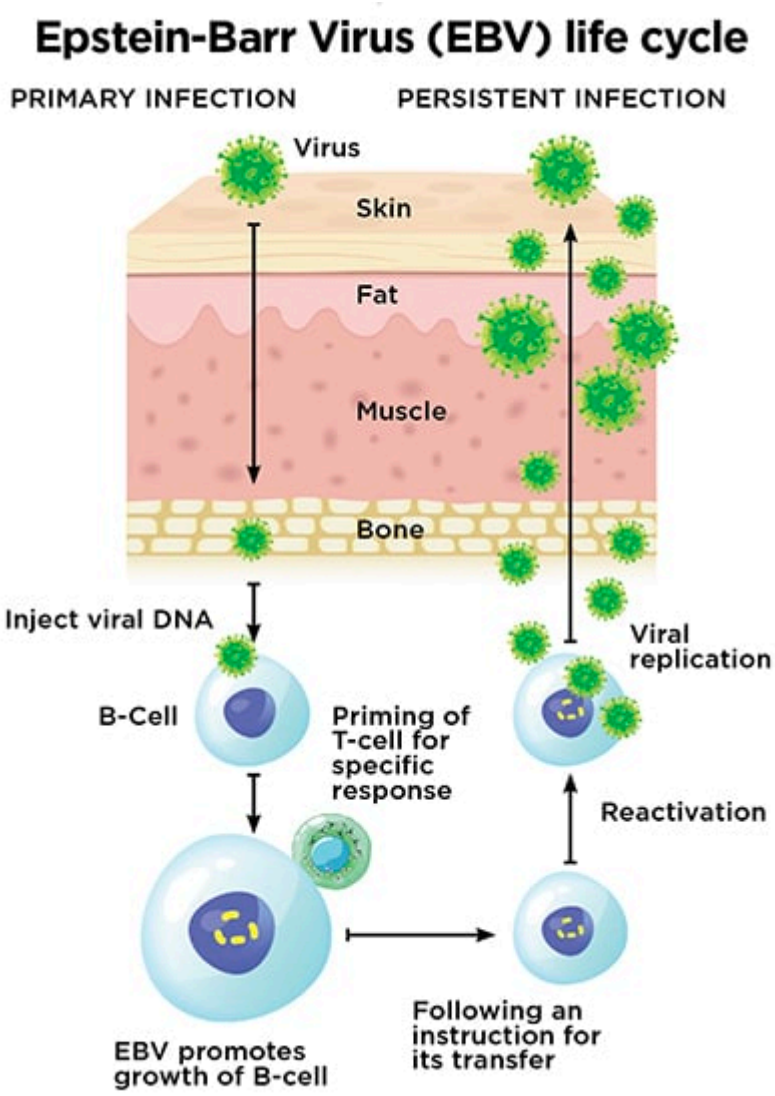
What do we know about the link between Epstein-Barr virus (EBV) and multiple sclerosis? Is EBV a cause of MS? How does it interact with other known risk factors? Could recent investigations into the link between EBV and MS lead to new ways to prevent or treat MS? Three experts provide up-to-date information on an intriguing area of MS research.

What is EBV?
EBV is an extremely common virus — about 95% of American adults have been infected by the time they are 40 years old. Sometimes, EBV infection causes a mild childhood disease that resembles many other viral infections. Symptoms can include fever, fatigue, sore throat, swollen lymph nodes and a rash. If adolescents or young adults are infected with EBV, it can cause infectious mononucleosis ("mono"). But many people never know they've been infected, and EBV can remain silently in their bodies for the rest of their lives.

EBV and the development of MS
Researchers have long known there is a link between EBV infection and the later development of MS, according to Bruce Bebo, PhD, executive vice president of research for the National Multiple Sclerosis Society.

"Having infectious mono as a teen is linked to a greater risk for later development of MS as an adult," he says. "But this is a complex issue. Development of MS likely involves genetic, immunological and environmental factors. EBV may be an important necessary step, but only

a very small number of people exposed to EBV go on to develop MS, so we still have a lot to learn."



Epstein-Barr virus (EBV) life cycle.

A recent large study in active-duty U.S. military personnel has more clearly identified EBV infection as a major risk factor for MS. Alberto Ascherio, MD, professor of epidemiology and nutrition at the Harvard T. H. Chan School of Public Health and a professor of medicine at the Harvard Medical School, and his colleagues looked through 20 years of medical records of more than 10 million young adults in the military and identified 955 who were diagnosed with MS during their service. The researchers examined blood samples from these individuals and control individuals who did not develop MS, looking for evidence of EBV and other viral infections.

The key findings: "EBV infection increases the risk of developing MS by over 30-fold in this population," Ascherio says. "To put this in perspective, other risk factors clearly contribute to the development of MS, including genetic predisposition, vitamin D insufficiency, cigarette

smoking, childhood obesity, etc., but each of these other factors increase risk in the range of about two-fold." Moreover, risk of MS was not increased by infection with other viruses the researchers looked at.

William H. Robinson, MD, PhD, chief, Division of Immunology and Rheumatology, and professor of medicine at Stanford University, has published a possible explanation of why EBV and MS are linked.

"We found very strong evidence for a role for EBV in triggering MS through what we call molecular mimicry," Robinson says. "Certain proteins inside the virus are similar to proteins in the myelin sheath in the brain. This similarity can trigger cross-reactivity in our immune responses. The immune system attacks EBV to try to clear the virus, but when it does this, it can also mistakenly attack those similar brain proteins, damaging the myelin sheath and causing the short-circuiting of nerve signals that results in the numbness and muscle weakness typical of MS."

Prevent EBV infection, prevent MS?

Both Ascherio and Robinson say their results suggest that if we could vaccinate babies or children and protect them against EBV infection, then we might be able to prevent MS in the future, although more research is needed to prove this. Also, no EBV vaccines are currently available, although scientists are working to develop them. Moderna Inc., which used novel mRNA technology to create successful COVID-19 vaccines, adopted that same approach to create a new vaccine that targets 4 EBV proteins and is designed to prevent infection. This vaccine is being tested in a phase 1 clinical trial to evaluate its safety and the best dose to use. In addition, Moderna is studying a different mRNA vaccine designed to control EBV in people who have already been infected. It has not yet entered clinical trials. The NIH is also creating EBV vaccine candidates, and one is in phase 1 clinical trial testing.

Bebo points out that while EBV appears to be a major factor in developing MS, other risk factors are involved.

"It is likely that EBV is one part of a sequence of events that needs to happen," he says. "Picture the development of MS as a series of dominoes. If you remove one, then the rest of the dominoes won't fall. If EBV infection is a critical step in the sequence, then maybe removing this key domino will prevent MS."

Could EBV cause MS progression?

Is EBV infection involved in MS progression and/or relapse? "This is a much more speculative question," Robinson says. "EBV very well could be involved in later stages of MS, but that's not yet been demonstrated. Perhaps if you have persistence of this molecular mimicry, maybe that promotes progression of MS. If so, targeting EBV in people with MS might have benefit, but that's highly speculative, and it's not supported by data to date."

He emphasizes that people with MS should not be looking for ways to treat EBV at this time.

“There is no real data to indicate that targeting EBV in people with established MS is helpful, but there is considerable research underway to investigate this question,” he says. For example, Atara Biotherapeutics is testing a therapy that can specifically identify and destroy only the B cells infected with EBV. This phase I/II (very early stage) trial is underway in people with progressive MS to see if removing these B cells will slow disease progression.

Robinson and Ascherio also explain that if EBV infection is proven to be linked to MS progression or relapse, then perhaps this knowledge could be used to create new therapies, such as a therapeutic vaccine or antiviral agent that could modify the immune response to existing EB virus infection. Robinson points out that there already is a similar type of vaccine, the herpes zoster vaccine, that prevents shingles in older people who have had chicken pox as children and are already infected with the herpes zoster virus.

Future research

The Society has long supported a wide variety of studies in the immunology of MS and provided some of the financial support for the recent Ascherio publication, as well.

“An important next step is to lay the groundwork for a prevention trial that will determine whether preventing infection with EBV in populations that are at high risk of developing MS will block the development of MS,” Bebo says. “The Society will engage with global experts in viral causes of disease and clinical trials to determine how best to perform these studies.”

Both Ascherio and Robinson plan additional investigations into MS and EBV. Ascherio’s research group is asking whether they can predict which individuals infected with EBV will go on to develop MS.

“We are trying to find biomarkers — molecules in the blood — that identify those people so we can intervene and target them before MS develops,” Ascherio says.

His group is also in the very early phases of designing and seeking funding for trials to determine whether antivirals will help modify the course of MS, but Ascherio emphasizes that these trials, if funded, will not start for two to five years.

Robinson says his team is already involved in or planning multiple studies to learn whether EBV infection promotes the progression of MS.

“It’s an exciting time,” Robinson says. “I think this latest research represents a transformational advance in our understanding of MS. The best way to develop more effective MS therapies is to understand the fundamental basis for the disease and to leverage those insights to develop next-generation therapies.”

Mary E. King, PhD, is a medical writer in Boulder, Colorado.

Learn more about the link between MS and the Epstein-Barr virus.