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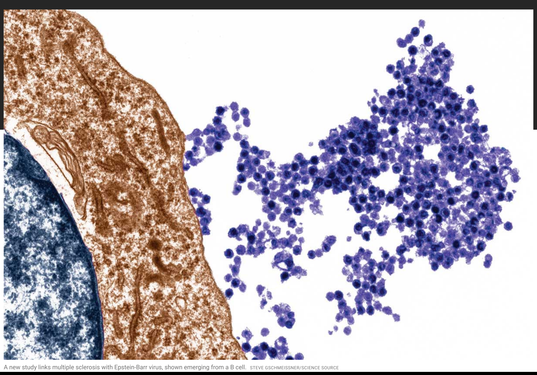
Two decades of soldiers' medical records implicate common virus in multiple sclerosis

Vaccines under development against Epstein-Barr virus might prevent rare, devastating disease

13 JAN 2022 · 2:00 PM · BY JOCELYN KAISER



A new study links multiple sclerosis with Epstein-Barr virus, shown emerging from a B cell. STEVE GSCHMEISSNER/SCIENCE SOURCE

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One hundred and fifty years after a French neurologist first recognized a case of multiple sclerosis (MS) in a young woman with an unusual tremor, the cause of this devastating disease remains elusive. Now, a study that combed data from regular blood tests of 10 million U.S. soldiers has found the strongest evidence yet that infection with a common virus, Epstein-Barr virus (EBV), dramatically increases a person's chances of developing the rare disease.

The work leaves many questions, such as why MS only affects about one in 1000 people even though nearly everyone will contract EBV in their lifetime. Still, "It provides probably the best evidence that can currently be obtained for a major pathogenic role of EBV in MS," says neurologist Hans Lassmann of the Medical University of Vienna, who was not involved in the study.

The study authors hope it will spur the development of a vaccine against EBV. The virus has been linked to several cancers and causes mononucleosis, and early vaccine testing is underway. Researchers then want to test whether vaccinating young people against EBV prevents MS.

MS develops when immune cells go awry and attack the myelin sheaths that insulate nerve fibers in the spinal cord and brain. The result is vision problems, pain, weakness, and numbness that can come and go, but worsen over time. Infusions of antibodies that deplete B cells, a type of white blood cell, can curb relapses. But the disease has no cure.

A combination of genetics—the disease often runs in families—and environmental triggers such as viruses is the likely cause. EBV, a herpesvirus that infects most people by adolescence and then lies latent in B cells throughout life, has long been a prime suspect. People who have had mono are at higher risk for MS. But although 99% of MS patients have had an EBV infection, 95% of those without MS have, too, making it difficult to pin down the virus' effects.

Ideally, researchers would track a group of young people who haven't yet been infected by EBV to see whether those who contract the infection are more likely to develop MS than those who don't. A team led by physician and epidemiologist Alberto Ascherio of the Harvard T.H. Chan School of Public Health found a clever way to do that. They probed a medical records database of 10 million active duty U.S. military personnel who enlisted between 1993 and 2015 and gave a blood sample every other year for HIV testing.

Eventually, 955 soldiers developed MS. Of the 801 with sufficient blood samples, 35 were negative for EBV in their first blood test; all but one became EBV positive during the study before developing MS on average 5 years later. By comparison, only half of 107 MS-free study participants used as controls became EBV positive during the same period, the researchers report today in *Science*. That means an EBV infection multiplies a person's risk of MS 32-fold, comparable to the increase in risk of getting lung cancer from heavy smoking, Ascherio says.

None of the other common viruses Ascherio and his team tested for showed an effect. To bolster their case, they showed that people who eventually developed MS had a rise in levels of a protein linked to neural degradation after their EBV infection. Ascherio believes the study clinches the case. "How do you explain the fact that you don't get MS unless you get EBV? There is no other alternative explanation," he says.

Others are cautious. The new evidence is "very exciting," but "it's still an association," says Jeffrey Cohen, a virologist at the National Institute of Allergy and Infectious Diseases. And the study doesn't explain why most people who get EBV don't develop MS, says neurologist Emmanuelle Waubant of the University of California, San Francisco. "Clearly other fuses have to be lit for the trigger to result in the disease," says Stanford University neuroimmunologist Lawrence Steinman, who co-authored a Perspective on the paper.

Also dissatisfying is the lack of a known mechanism for how EBV might cause the immune attack. Some researchers suspect EBV transforms B cells so they become pathogenic; others, including Steinman, suggest an EBV protein resembles a neural protein and teaches the immune system to attack nerves.

An EBV vaccine could help researchers prove the virus has a causal role by vaccinating a large cohort of young people at high risk for MS because of family history. Experimental evidence that a vaccine prevents cases would "tick the final box," says neurologist Gavin Giovannoni of Queen Mary University of London, who is working with the MS patient community to design such a study.

Several years ago, GlaxoSmithKline developed a vaccine based on an EBV envelope protein but abandoned it after a trial showed it reduced the incidence of mono but didn't prevent EBV infections. Two new candidate vaccines now in early clinical trials could be more potent. One developed by Cohen displays the same EBV protein on nanoparticles. Another from Moderna contains messenger RNA that instructs cells to make four different EBV proteins.

Vaccine expert Larry Corey of the Fred Hutchinson Cancer Research Center cautions that despite the potential public health benefits, there's no guarantee a company will take an EBV vaccine through licensing. Still, the new evidence firming up the role of EBV in MS "should make the risk benefit of that investment much greater," he says.

Correction, 13 January, 2 p.m.: An earlier version of this story misstated the range of enlistment data used in the study.

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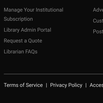

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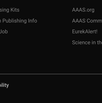

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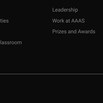

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