

Transcript Details

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Exploring Genetic Links Between EBV Clearance and MS Risk

Announcer:

Welcome to *NeuroFrontiers* on ReachMD. On this episode, we'll hear from Dr. David Hafler, who's the William S. and Lois Stiles Edgerly Professor of Neurology and Professor of Immunobiology at the Yale School of Medicine. He'll be discussing how genetics affecting Epstein-Barr virus clearance may drive multiple sclerosis. Here's Dr. Hafler now.

Dr. Hafler:

So what do we know about the potential cause of MS? The breakthrough work by Alberto Ascherio published in *Science* showed that when looking at army recruits with their yearly blood samples, in almost all—not every, but almost all—instances before the onset of MS, the EBV infection averaged about seven years between EBV infection and the onset of MS. And we know that 100 percent of patients with MS have been infected with EBV, whereas only about 93 percent of the general population is infected with EBV. We and others have looked very hard for EBV in the brains of patients with MS and in the B cells and really can't find any significant amounts of EBV in MS brain compared to controls. And also, if you look for EBV in the peripheral blood of patients with MS by very sensitive techniques at the time of diagnosis, again, there may be some EBV with relapse that's being studied now, as before the relapse. Only about 15 percent of patients have any detectable EBV in the blood, in the B cells, and it's mainly in the latent and lytic form.

So we did a study where we used the UK Biobank and all of us where there have been sequences of DNA of hundreds of thousands of individuals, and we're able to detect EBV in the DNA sequencing as a contaminant. The episomes of EBV are contaminating the DNA being sequenced, so that becomes a phenotype. And by developing a technique to identify the virus, we can ask, are there genes associated with the persistence and ability to clear the Epstein-Barr virus? And it turns out we could identify 39 genetic variants, common variants, and they are associated with the inability to clear the virus.

When we looked at those variants, we found there was an incredible overlap with the MS genes part of the International MS Genetics Consortium, which led to the discovery of the genes associated with risk of developing MS. And it turns out that there is an overlap at a p-value of ten to the minus twelve between the genes that cause MS and the genes that do not allow one to clear Epstein-Barr virus. These data would suggest that the Epstein-Barr viral infection in adolescents—not in children, but adolescents—leads to a hyperactivated immune state of B cells in patients with a genetic risk of MS. And this makes the B cells the adjuvant, which breaks tolerance, allowing for autoreactive T cells to attack the brain. So we believe the key event is occurring at the time of infection, and it's related to the genetics.

So though most of us have been infected with the Epstein-Barr virus, it's the genetics which do not allow one to clear the virus properly with a hyper B cell response that breaks tolerance; that may lead to the disease.

So that's the working model right now. And the plan is to do studies of adolescents with high genetic risk of MS and children of patients with MS. We'd follow them very carefully for the onset of Epstein-Barr viral infection, and then monitor the immune system for autoreactivity, persistence of EBV, and activation of B cells to see if that's really associated with the genetic makeup of the individuals, and perhaps in the future, even try to do a vaccination with an EBV vaccine.

Announcer:

That was Dr. David Hafler talking about how genetics involving EBV clearance could drive MS. To access this and other episodes in our series, visit *NeuroFrontiers* on ReachMD.com, where you can Be Part of the Knowledge. Thanks for listening!