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# The Evolution of Epstein-Barr: Can it Lead to MS?

**Announcer:**
Welcome to *Innovations in Medicine,* sponsored by Moderna. This is a non-certified educational series produced and controlled by ReachMD and is intended for healthcare professionals only. Here's your host, Dr. Charles Turck.

**Dr. Turck:**
Multiple sclerosis, or MS, affects about 2.8 million patients worldwide. This progressive disease can be disabling, even fatal, and there's currently no cure for it. But a recent development in our understanding of the Epstein-Barr virus and mRNA therapeutics may help us develop a vaccine to prevent MS.

Welcome to ReachMD. I'm Dr. Charles Turck, and joining me today to explore the role of mRNA therapeutics in MS is Dr. Ahmed Obeidat, who's an Associate Professor in the Department of Neurology, and Director of Immunology and the MS Fellowship Program at the Medical College of Wisconsin. Dr. Obeidat, thanks for being here today.

**Dr. Obeidat:**
Thanks for having me.

**Dr. Turck:**
Before we dive into MS, Dr. Obeidat, let's take a look at the Epstein-Barr virus. Would you give us a brief overview of it?

**Dr. Obeidat:**
Certainly. So, the Epstein-Barr virus is a gammaherpesvirus. So, it's one of the viruses of the herpes family. And those viruses tend to infect humans, tend to stay in the human body for a long time, so we call it a latent infection. For example, Epstein-Barr virus would infect the host, who is a human. It's going to stay in forever, we think, as a latent infection, so it tends to live in what we call the B lymphocytes, or specifically, memory B cells. So, the virus infects and invades those cells, and then tend to stay there and escape immune surveillance. So, it's important that the virus has many ways to be able to escape immune surveillance, and live in the human being for decades and this is, in part, related to some of the proteins on the virus and ways the virus can invade the immune system. So, one of the things about Epstein-Barr virus as a gammaherpesvirus, is when it is acquired, it's typically acquired early in childhood. So, there are two peaks when the virus is acquired of age for humans, so one peak is early in childhood, and another peak is in adolescence. So, by the time we are adults, the majority of us are infected by the virus. In fact, over 90 to 95 percent of humans when they're adults, they're actually infected by the virus based on some studies. So, this is important to know and, kind of think about, as we think about strategies to battle this virus, because we have to intervene early, to be able to maybe prevent the primary infection with this virus. But one of the things also, if the virus is kind of already infected the human being, then we may be able to develop some strategies to better control this infection, and maybe that's where we maybe also focus when we talk about this virus later today.

**Dr. Turck:**
And if we put this in the context of MS, what kind of impact can the Epstein-Barr virus have on MS biomarkers?

**Dr. Obeidat:**
Yeah, so in the context of MS, it's interesting because for over 40 years, we actually knew that there is some association between Epstein-Barr virus and multiple sclerosis. But the causality was very hard to determine, and people thought, "Oh, maybe Epstein-Barr virus is associated with MS, it could be part of the multiple risk factors," which we know it is now. And people have studied this over many years, and what really changed in the past, I would say, few years, mainly earlier this year even and last year, is we are closer to knowing that the Epstein-Barr virus may be actually a cause of MS. Maybe there is a causality there. So, one of the important things to

know is in MS there are several biomarkers. Some of them are imaging-based biomarkers, some of them are serum-based or blood-based biomarkers, and some of them are spinal fluid biomarkers. And, when we think about multiple sclerosis itself, multiple sclerosis when it develops, we can use those biomarkers to help diagnose MS, but also we use these biomarkers to follow the trajectory of multiple sclerosis and the disease activity. But how it relates to Epstein-Barr virus is very important, because what we know now from most recent studies mainly done by the Harvard group where they looked at a large database of people in the military in the U.S., so about ten million people. And those people have five percent of them were not infected by Epstein-Barr virus at the time when they joined in the military and the time when they started to get blood samples from them. And then they tend to get more blood samples over time, and what they found is that people who were negative, or not exposed to the Epstein-Barr virus, they needed to become positive, so serial-convert, meaning that they become positive for Epstein-Barr virus before developing multiple sclerosis. There are about 55 patients who met this. So, what happened is, based on these data, we know that the virus infections happened before the disease developed, which is important because if you want to determine causality, you want the positive agent to happen before the actual ultimate effect, which is the disease here, right, or multiple sclerosis. But in relation to biomarkers, there are some biomarkers that people use to look at neural inflammation, or a neural damage. One of them is called the neurofilament light, and in this same study, what they found, the authors and the investigators, they found that the level of serum neurofilament light which is a marker of neuroinflammation and neural damage, went up prior to the clinical onset of MS, but also went up after the infection with Epstein-Barr virus. So those patients, at the time they were not MS diagnosed, but those people who later moved into develop MS, their levels of this biomarker were similar to people who did not have MS. And then, at the time when they had the infection with the virus, this level of that serum neurofilament light went up, indicating the start of a biological process that is destroying or having an effect on the central nervous system.

So, this is important because we know that the virus infection happened before this biomarker went up, and then diagnosis of MS happened, so, sometimes up to six years prior to the clinical onset of MS. So that's pretty convincing evidence, that the virus has a role in the development of the change in these biomarkers, but also in in multiple sclerosis development.

**Dr. Turck:**
For those just tuning in, you're listening to ReachMD. I'm Dr. Charles Turck, and today I'm speaking with Dr. Ahmed Obeidat about our understanding of MS. Let's switch gears and take a look at the mRNA 1189 vaccine in development. Dr. Obeidat, what could you tell us about it?

**Dr. Obeidat:**
It's an early stage vaccine. It's in phase 1 clinical trial. I think launched in January of 2022, and it is trying to utilize the same technology that now we are familiar with because of the COVID-19 pandemic, which is the mRNA-based vaccination. And this is important because this technology has existed really for decades, and for many years. But because of the COVID-19 pandemic, the technology was accelerated, and then now, we have it as a technology that we can utilize with the COVID-19 vaccinations. One of the important aspects of this, as in the pandemic, like the COVID-19, the vaccine was able to help tremendously with decreasing the new infections, decreasing the severity of infections for people around the world. So, the benefits of this type of vaccination, this technology, is evident now, right? So, one of the things that trying to purpose this technology again, or repurpose this technology for other vaccinations, including the Epstein-Barr vaccine. So, this is an early, phase 1 study, that is trying to look at the safety of the mRNA vaccine. But also, what is the proper dose? What is the appropriate dose to be used? So, they're trying to set multiple-dose strategies, to see in the adults, how can we maybe use this vaccine to protect from Epstein-Barr virus infection, but also maybe to better control the viral infection itself in people who already got exposed. So, this is important, because the mRNA vaccine technology now is proven. Now, people are more I would say accepting of this technology, right? Early on, we know controversy around some of the aspects, but then now we know that this has proven scientifically to be a strategy that worked in COVID-19 vaccination, and now they're trying to see if we can utilize this same technology to be able to prevent Epstein-Barr virus.

**Dr. Turck:**
Now, before we close, Dr. Obeidat, do you have any final thoughts or takeaways you'd like to share with our audience?

**Dr. Obeidat:**
We kind of emphasized in this talk is multiple sclerosis is a really common, relatively very common disease in the young adults. And it's one of the most common causes of neurological difficulties and disability in the end. So, the disease really impacts many people around the world, I think is more than 2.8 million, or more than that, at least, right. And, in the United States, we know it's about one million people living with MS. But it doesn't only impact the people who live with MS. It impacts their loved ones, impacts people live around them, impacts their whole community. So, this is a very important disease. So, when we think about strategies, could it be one day where we'll be able to decrease the incidence of MS. That's huge. That's going to be very important, because when we think about this disease and its impact, if we're able through a vaccination through the technology of the mRNA or other technology. If we are able

through this vaccination to either prevent primary infection, or better control the infection, then we may be able to impact multiple sclerosis, among other diseases, including lupus and including cancer, right? So, this is something that we're hopeful to see. One of the things that's important to know is there are multiple other causes of MS, right? So, Epstein-Barr virus is one of the ones that has causality, but there are multiple others that we think are risk factors, maybe not yet established to that causality kind of a level, but including smoking, including low vitamin D, including genetic variants – there are over 200 genes associated with MS. And then some other toxins, and solvents, and other things that are in the environment. So, in a way, if we are able to, maybe affect one of the important, or key aspects of the pathogenesis of MS, which is Epstein-Barr virus, maybe then the other risk factors may not be able to actually move forward to develop MS, because we know that infection with EBV is necessary, but we know it's not sufficient for the development of MS. So it's an integral part of what leads to multiple sclerosis, so if we're able to control that aspect, if we're able to prevent it, or able to better control it, as we said before, then maybe we will have a much better impact in the community, and maybe we'll be able to prevent cases of MS in the future, which is going to take decades for us to know if the vaccine has an impact, but we are hopeful that if we're able to get a safe vaccine, that is able to control the infection or prevent primary infection, we may be able to, 30 years from now, 40 years from now, may see a decrease in the incidence of MS.

One can be very hopeful and say maybe we'll prevent MS, but that's going to be unlikely, just because of the odds of people not everyone gets a vaccine and is going to get, protection from the virus infection, or better control or a good response. So, this is why we may still see cases of MS, but hopefully we'll be able to reduce the number pretty significantly.

**Dr. Turck:**
This has been a fascinating look at how mRNA therapeutics might be applied to progressive diseases like MS. And I want to thank you, Dr. Obeidat, for sharing your insights into this novel therapeutic avenue. It was great speaking with you today.

**Dr. Obeidat:**
Yeah, same here. Thank you very much.

**Announcer:**
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