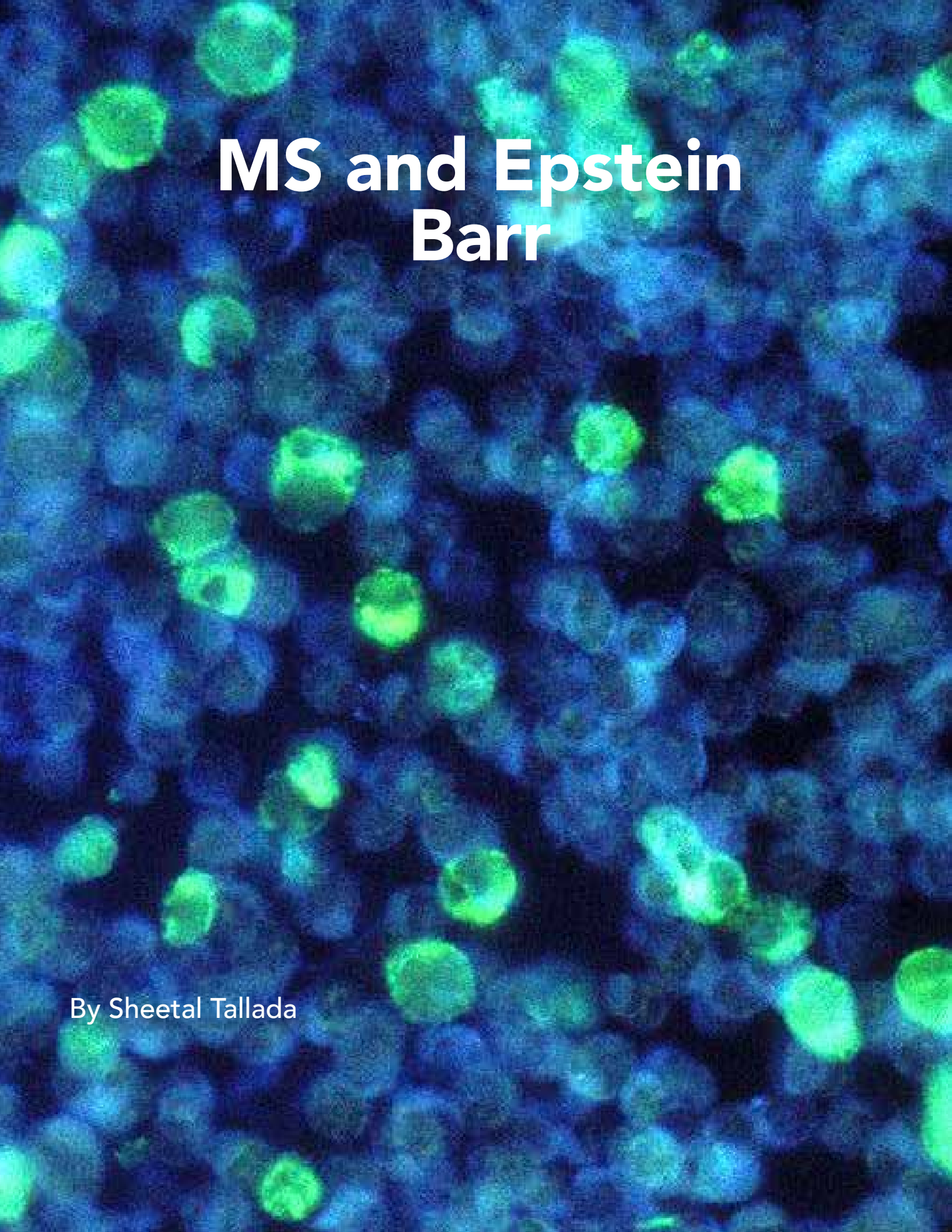

MS and Epstein Barr

By Sheetal Tallada

Imagine: you're in the middle of a New Year's Eve party hosted by the managers at your job. You have been dancing all night, you are especially in the mood, and you have been craving a cocktail. You already had two, so why not get a third? But, there's a huge crowd at the bar and you really don't want to wait. However, your co-worker just grabbed a nice martini from the bar. As your coworker comes up to you and claims that this is the "best drink ever," you take the glass from them and quickly finish it. They walk away in disappointment, saying phrases such as "you're selfish" and "why would you do that?!" You casually ignore their comments, and continue to dance the night away.

Four weeks later, you are getting ready for your yearly one-on-one meeting with your manager so they can track your progress. But something doesn't feel right. For the last week, you've had a constant headache, not to mention unrelenting fatigue. You've been passing it off as a stress response to this meeting, but today you feel significantly worse. You have a 104 degree fever, rashes up your forearms, and a swollen neck. You end up skipping your meeting, spending your Friday evening in the emergency room instead. Eventually, the doctors diagnose you with Infectious Mononucleosis (mono).

As you recover from mono by laying in bed all day, missing meetings, and using up all of your sick leave, you try to figure out how this could have happened. After doing some research, you see that the main method of contracting mono is through shared saliva. Maybe it was from the cocktail you stole from your coworker! But this confuses you: nobody at work you are close with exhibited or talked about having a cold… why are you suffering from these harsh symptoms?

Infectious mononucleosis is a common infection that gives you cold-like symptoms that can last up to a month. Infectious mononucleosis is one of several illnesses that can be caused by Epstein-Barr virus (EBV), also known as human herpesvirus 4. EBV is one of the most common human viruses, and infects 95% of the population at least once in their lives [1]. However, the illness most commonly caused by EBV is Infectious Mononucleosis. According to a case study from the University of Minnesota, over 25% of adolescents and young adults get symptomatic Infectious mononucleosis due to primary Epstein-Barr virus infection.

What is alarming and not as freqently discussed, is that EBV is also correlated with many other diseases. When you get EBV, it stays in your body for the rest of your life, even if you aren't contagious or symptomatic. Based on current research, underlying EBV can lead to many dangerous disorders and diseases, and its associated prevalence rate is high (Table 1) [2].

In table 1, we see that cancers such as Nasopharyngeal carcinoma are highly prevalent due to the infection of EBV. We can also see that over 99% of Mono cases are caused by the Epstein Barr virus. However, groundbreaking research has shown that EBV is actually highly correlated with one additional debilitating disease: multiple sclerosis (MS).

All about EBV

Epstein-Barr Virus is the first isolted human tumor virus [3]. It was discovered in 1964 by Drs. Anthony Epstein and Yvonne Barr, who discovered a cancer called Burkitt lymphoma. Burkitt lymphoma was the first cancer proven to be caused by a virus, which led to future research on virus-cancer relationships. As a result, researchers were inclined to learn more about EBV itself and how it could

Table 1

Disease	Percentage
Infectious mononucleosis	> 99%
Oral hairy leukoplakia	> 95%
Hodgkin's disease (all subtypes)	40%
Hodgkin's disease (AIDS-related)	> 95%
Non-Hodgkin lymphoma (all subtypes)	5%
Non-Hodgkin lymphoma (AIDS-related)	40%
Burkitt's lymphoma (Africa)	> 95%
Burkitt's lymphoma (North America)	20%
Burkitt's lymphoma (AIDS-related)	30%
Nasopharyngeal carcinoma (Asia)	> 99%
Nasopharyngeal carcinoma (North America)	75%

Table 1: Percentage of cases of specified disease due to the infection of EBV (created by Sheetal Tallada, data from [2]).

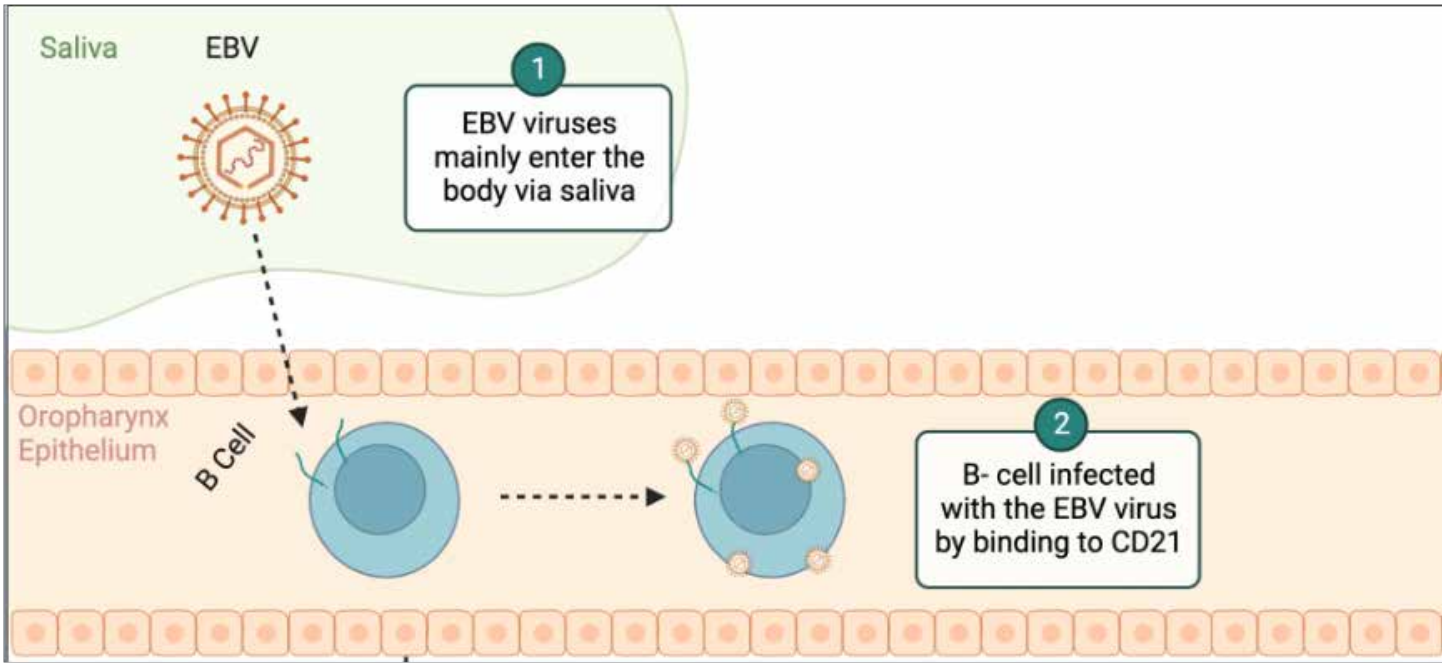

Figure 1: Pathway of how the EBV virus ends up entering the human body and infects B-cells.

possibly affect the immune system. Researchers have even investigated how EBV might lead the immune system to deviate from its main function: protecting the human body [4].

Understanding how EBV infects the immune system is vital in order to understand how it can eventually lead to deadly diseases. EBV exists mainly in two types: EBV-1 (Type A) and EBV-2 (Type B). Although their genetic code differs slightly and their mechanisms of infecting the immune system vary, they have one thing in common: they infect B-cells (EBV-2 does not infect them as efficiently as EBV-1) [5].

B-cells are an important component of the immune system. They are a white blood cell that is responsible for making antibodies [6]. These antibodies are responsible for identifying and binding to a "foreign object," such as a pathogenic bacteria or a virus, thus identifying the object to the rest of the immune system. EBV disrupts this process by attacking B-cells. The figure below presents how EBV eventually enters the immune system (Figure 1) [7].

After EBV attacks the B-cells by binding to their receptor, the B-cell eventually incorporates the DNA of the virus into the cell. As a result, the B-cell will begin to reproduce the virus, allowing it to spread throughout the body.

Once someone is infected, the virus may never truly go away, and can also become reactivated under stressful life conditions, when taking immunosuppressants, or as a result of hormonal changes. Long-term, EBV can cause an overactive immune system, which can in turn lead to disorders such as Infectious Mononucleosis and Multiple Sclerosis. EBV can also weaken the immune system, leading to cancers such as Burkitt's Lymphoma or Nasopharyngeal Carcinoma [8].

All about Multiple Scerosis

Multiple Sclerosis (MS) is a neurodegenerative disorder that can lead to motor dysfunction, numbness, weakness in the limbs, tremors, problems with coordination, and unsteady gait [9]. MS can also lead to vision problems, such as blurry vision and, in severe cases, loss of vision; other symptoms include dizziness and fatigue. Fewer than 1% of the population is affected by MS in the United States. Although people can have fulfilling lives even with MS, many patients have a reduced quality of life. MS patients live 5 to 10 years fewer than the average. As a result of MS, the protective coating around neurons (the myelin sheath), is degraded. Myelin is a fatty substance that coats neurons; its main role is insulation, protecting, and speeding up communication between neurons. When the immune system is overactive, as is the case in MS, it sometimes attacks and damages the myelin sheath, (Figure 2) [10].

Multiple Sclerosis (MS) can lead to motor dysfunction, such as numbness and weakness in the limbs, tremors, coordination problems, and unsteady gait [9].

MS can also lead to vision problems, such as blurry vision and loss of vision in severe cases. Other symptoms include dizziness and fatigue. Although people can have fulfilling lives even with MS, many patients have a reduced quality of life. Furthermore, MS patients live 5 to 10 years less than the average person. Less than 1% of the population is affected by MS in the United States.

There are four types of multiple sclerosis:clinically isolated syndrome (CIS), relapsing-remitting MS (RRMS), primary progressive MS (PPMS), and secondary progressive MS (SPMS). CID is the least debilitating, while SPMS is the most debilitating. Out of all of these types, the most common type of multiple sclerosis is RRMS. In RRMS, there are periods of time where the MS patient has worsening symptoms and then periods when they recover and have minimal to no MS symptoms.

Multiple sclerosis is classified as a T-cell mediated autoimmune disease [11]. T-cells are also white blood cells and in general help to combat against foreign substances that enter the immune system. They are slightly more complex than B-cells, as there are two types of T-cells. Helper T-cells encourage B-cells to make antibodies, and also promote the production of the second type of T-cells, Killer T-cells. Killer T-cells are responsible for killing cells that have been infected by a foreign invader. With an overactive immune system, T-cells misinterpret the body itself as foreign, and attack it. The overactive immune system in MS is a persistent mystery, one that has prevented scientists from finding a proper treatment for this debilitating disease.

What is the connection between EBV and MS?

You might be wondering, "What do Epstein-Barr Virus and Multiple Sclerosis have to do with each other?" For a few years, researchers have been keen to know the causes of MS in hopes of finding a treatment. Genetic factors, low socioeconomic status, and environmental factors (such crowded, polluted living conditions) are correlated with an increased prevalence of MS.

A longitudinal case study, in accordance with the United States Military, examined the prevalence of EBV infections in patients with MS [12]. The researchers had access to over 10 million active-duty US military personnel serum samples, as everyone in the military is tested for HIV. The military keeps the residual serum samples in the Department of Defense Serum Repository (DoDSR), which gives researchers access to over 20 years-worth of data. After identifying serums with MS-positive individuals, the researchers created their comparison groups, by having 801 MS case samples and 1566 controls to assess the EBV infection status of each group. The study showed that, out of the 801 MS serum samples, 800 of them were EBV-positive. Furthermore, the researchers also used other serum samples within the 10 million samples and found that the risk of getting MS increased 32 times with EBV infection but NOT with other viruses. The researchers also examined levels of neurofilament light chain, an indicator which reveals if neuronal degeneration is occurring. What was really interesting is that these biomarker levels increased in the serums only with EBV infection.

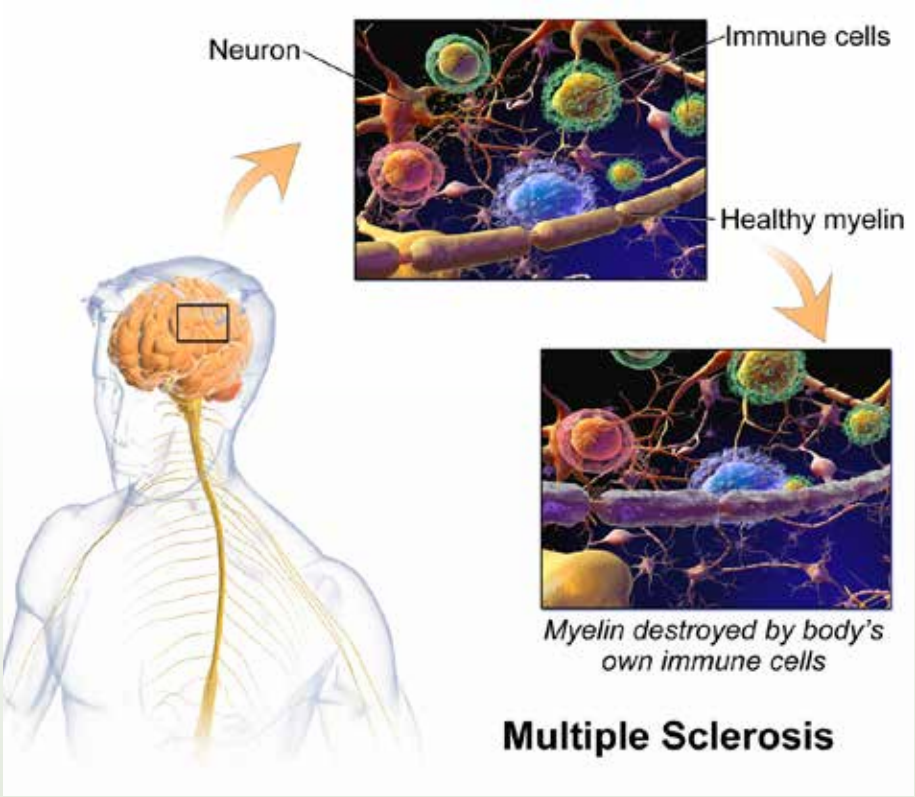

***Figure 2**: Illustration of Myelin sheath before and after the immune system attacks the CNS.*

Overall, the researchers concluded that there is a strong correlation between the presence of EBV and the onset of MS. After multiple comparisons with other viruses similar to EBV, they concluded that EBV is the leading cause of MS [12].

The longitudinal study stated above was published in January of 2022, making it one of the most recent major studies to find substantial evidence for EBV being the leading cause of MS. When 800/801 MS individuals have EBV virus in their systems, that equates to a 99.87% rate of MS patients that were EBV-positive [12].

The United States Department of Veteran Affairs has been very vocal about the prevalence of EBV not only in MS, but many other autoimmune diseases. A 2018 study looked at the levels of a protein called EBNA2, which is present in patients with EBV, and in patients with various autoimmune diseases. The researchers found that EBNA2 is associated with lupus, multiple sclerosis, rheumatoid arthritis, inflammatory bowel disease, type 1 diabetes, juvenile idiopathic arthritis, and celiac disease. Dr. John B. Harley, one of the lead researchers for this study, writes that one of the study's main findings was that "it is the body's immune and inflammatory response to the virus and to the infected cells that causes the conditions, rather than the virus directly [13]." But why might someone be predisposed to getting MS from EBV, even though 95% of the population has it? Why is it that only 1% of the US population suffers from MS, yet almost all of them have EBV? Why is it that 1 in 4 people suffer from mono, yet 99% of those cases are caused by EBV infection? EBV is responsible for many cancers and autoimmune disorders, but the rates of these diseases, especially severe versions, are significantly lower than EBV itself. There is more to these disorders than just EBV infection: whether a person is predisposed to getting these diseases is also an important factor.

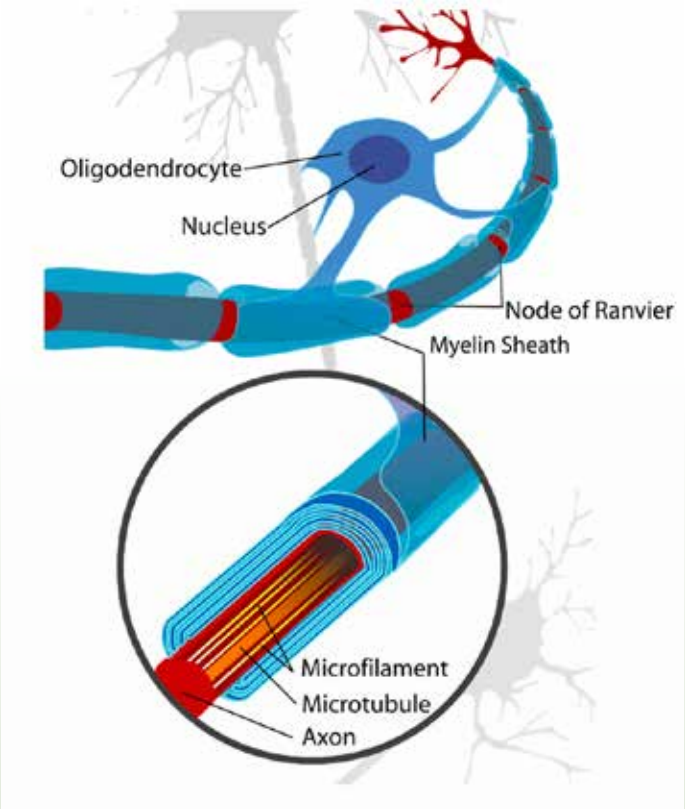

***Figure 3**: Diagram of Myelin Sheath surrounding neuron*

How do we get EBV to Multiple Scerosis

While 95% of a population is infected with EBV, only 25% of those people end up getting mono, and only ~1% of the EBV population gets MS. Meaning that the outcome of EBV varies from individual to individual.

One study focused on EBV infection with and without Infectious Mononucleosis that revealed some fascinating results. First, females go through puberty earlier than males and are more likely to start having intimate relationships earlier. Therefore they tend to contract EBV earlier than males. Females are also more likely to be caretakers for younger children (ages 0-3); those young children have a higher rate of exposure to other children's saliva, exposing their female caretakers to EBV [14]. Despite these findings, the researchers were not able to elucidate the specific factors that make EBV more likely to develop into mono.

Another study focused on socioeconomic factors rather than sex factors. This observational, millennium cohort study looked at children in the UK, and found that EBV infection rates were reduced in children living in small towns and rural areas regardless of SES. They also found that children living in overcrowded homes in urban areas, with low socioeconomic status, had higher rates of EBV in-

fection, even if they are not symptomatic. Families with material deprivation tend to have children that lack access to proper healthcare resources and end up being more likely to be exposed to EBV early on.

However, there have been few findings on which individuals are more likely to develop MS when infected with EBV. Still, MS has been correlated with low socioeconomic status. One study found that MS symptoms are more severe in those with a lower socioeconomic status. This is due to a lack of healthcare resources and preventative care. Since people with lower socioeconomic status are more likely to get infected with EBV at an early age, their immune systems are also more likely to be exposed to the virus for longer. And without preventative measures, autoimmune-like disorders are less likely to be caught and treated early on.

Overall, there is much more to learn about the mechanisms that lead EBV to progress into mono, or even progress into MS. However, groundbreaking research on EBV continues, making the possibility of new treatment options more likely every day.

Current Treatments/ Therapies

Although there is so much uncertainty about the mechanism of progress from EBV-Mono-MS, the current treatment options in clinical research trials cannot be ignored. Currently, there is an Immunotherapy study being conducted at the University of Queensland, in which the researchers have created a T-cell immunotherapy to give synthetic T-cells (ATA188). This is in hopes to give MS patients healthy T-cells via a stem cell transplant in order to eventually replace the affected T-cells in the patient. Even though this is a possible treatment and the researchers describe a well-supported mechanism by which the treatment would work, it has not yet been tested in clinical trials, and cannot be confirmed as a possible treatment mechanism until it has been approved [15].

A more generic treatment may come in the form of an EBV vaccine. Dr. Jessica Durkee-Shock of NIAID's Laboratory of Infectious Diseases has developed a vaccine that will begin clinical trials starting in June of 2022. This vaccine is going to be made with an iron-storage protein that is going to be able to attack a protein on the surface of EBV, called gp350, which will then allow for the human immune system to attack this virus and not bind as well to B-cells [16].

These treatments promise that there can be a EBV-based MS cure. They also promise that there might be a more accessible EBV preventative measure that arrests the EBV progression to Mono or even MS.

Given that most of the human population is already infected with EBV,. the progression of EBV to more serious disorders, such as MS, is highly concerning. Research is being conducted and treatment strategies are being created, ranging from immunotherapy to general vaccines. Studies show that higher rates of EBV infection and exposure occur to people of low socioeconomic status, people of color, and people in overcrowded spaces. When you are born in such circumstances that you cannot control, and especially living in places that do not offer proper healthcare access, it makes sense that these minority groups and low SES people are prone to getting infected at an earlier age. Living under high stress conditions also triggers the virus to become active again in the body, and this cyclical effect makes you prone to suffering from much more complex disorders caused by EBV. Science is one part of this, but the epidemiological aspect is severely underlooked at.

Even if we consider the scenario of the employee attending the New Year's party: this is probably the scenario for an average American trying to enjoy the benefits their employers provide after countless hours of work at their job. We ultimately do not know if this person will develop MS just by the details of the scenario. But even if they do, would the current healthcare system allow them affordable access to future immunotherapy treatments? And would they be able to access preventative treatments such as vaccines? These are all questions to consider about the future health of the human population in terms of MS, even if successful treatments are approved.

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