VARICELLA VACCINATION: A POTENTIAL STRATEGY FOR PREVENTING MULTIPLE SCLEROSIS

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ABSTRACT

Multiple sclerosis (MS) is a debilitating neurological condition affecting approximately 2.9 million people worldwide. Its cause remains unclear but environmental factors, such as post-childhood Epstein-Barr virus (EBV) infection, are thought to contribute to MS incidence. This study presents a new hypothesis that MS may be initiated by primary infection with clade 3 varicella-zoster virus (VZV) preceding primary EBV infection. The hypothesis may explain several MS epidemiological features: geographic variation in prevalence, changes in incidence and sex ratios over time, migration patterns, higher EBV and VZV seropositivity rates in patients versus healthy controls, extremely high MS rates in Sardinia, and identification of clade 3 VZV in a single MS patient. If validated, the hypothesis predicts exclusive detection of clade 3 VZV in MS patients, declining MS incidence in countries implementing universal childhood varicella vaccination since the early 2000s, and potential therapeutic benefits for existing MS patients from treatments that prevent herpesvirus reactivation.

KEYWORDS

Multiple Sclerosis, Varicella, Epstein-Barr Virus, Varicella-Zoster Virus, VZV genotyping

1. INTRODUCTION

Multiple sclerosis (MS) is a complex, inflammatory, degenerative disease affecting the central nervous system (CNS) in humans. Its exact cause is unclear but appears to involve genetic and environmental factors that trigger the destruction of CNS myelin. MS onset can occur at any age but generally occurs in adults between ages 20 and 45. The disease presents with diverse symptoms, such as visual disturbances, fatigue, muscle weakness, and sensory abnormalities, typically following a relapsing-remitting or chronic progressive course or a combination of these, resulting in impaired voluntary and involuntary bodily functions and lower quality of life.

Over 2.9 million individuals worldwide are living with MS, with the highest disease rates reported in northern Europe, Canada, the United States [1], and Sardinia [2]. Studies of concordance rates in identical twins indicate that genetic and environmental factors contribute significantly to MS risk [3], while rapidly increasing MS incidence and prevalence rates in some regions offer essential insights into the environmental triggers of the disease [2]. Nevertheless, some of these increases may be attributed to enhanced detection of MS cases due to improved diagnostic methods.

A comprehensive hypothesis for MS causation must explain several disease features: MS is a rare human CNS condition affecting about 1 in 3000 globally and 1 in 300 people in high-risk areas. Prevalence rates worldwide range from 0 to 330 cases per 100,000 population and show considerable geographical and ethnic variability. Historically, MS incidence was thought to align with a latitude gradient featuring the lowest rates in equatorial regions increasing toward the

poles, although this gradient may be diminishing [1,4]. MS rarely occurs in children and the elderly and is diagnosed more frequently in Caucasians than in Asians and Africans, while MS rates have risen among various ethnic groups and in countries historically free of the disease [1]. Concordance rates for MS in identical twins are at most around 30% [3], underscoring the importance of environmental factors in triggering the disease.

Epidemiological studies point to several observations that any hypothesis of MS causation must address. For example, numerous studies have implicated infections in disease development [4], such as those focusing on the reported MS epidemics on the Faroe Islands from the 1940s through the 1990s, and more recent studies investigating unexpectedly high MS prevalence rates in Sardinia, an island in southern Italy [2]. Migration studies indicate that MS risk is significantly influenced by migration age and original and final residence locations. Moreover, the female-to-male ratio of MS cases has shifted from 1:1 to over 4:1 in some regions in recent decades [1,4].
Studies have established a strong connection between Epstein-Barr virus (EBV) infection and MS, with past EBV infection leading to an up to 32-fold increase in disease risk [4-6]. MS is rare in regions where EBV infection occurs very early in life [4,7], and a history of infectious mononucleosis (IM) during adolescence has been associated with increased MS risk [8] but is not shared by all patients. Additionally, evidence suggests that at least two environmental factors contribute to MS causation [4,5,9,10], highlighting the need for a multifaceted approach for identifying specific factors associated with MS pathogenesis.

2. TWO POSSIBLE ENVIRONMENTAL MS TRIGGERS

Despite extensive research, MS's exact cause is unknown but appears to encompass multiple genetic and environmental risk factors. Intriguingly, migration studies have revealed that relocating from regions with low to high MS risk does not increase disease risk as dramatically as moving from high- to low-risk regions, indicating protective childhood environmental factors against MS may exist in low-risk areas. Furthermore, a study of temporal-spatial clustering of MS cases in Sardinia, Italy concluded that MS induction requires two triggers: one acting at least 21 years before MS onset and another just before disease presentation [10].

In addition, Epstein-Barr virus (EBV) infection has drawn significant attention as a potential disease risk factor, with compelling evidence linking delayed EBV infection (occurring in adolescence or later) to MS [4-6]. This study proposes that MS may result from two environmental triggers acting in a specific sequence: an initial infection by clade 3 varicella-zoster virus (VZV), followed by primary EBV infection. The rationale behind this hypothesis is summarized in the flowchart shown in Figure 1.

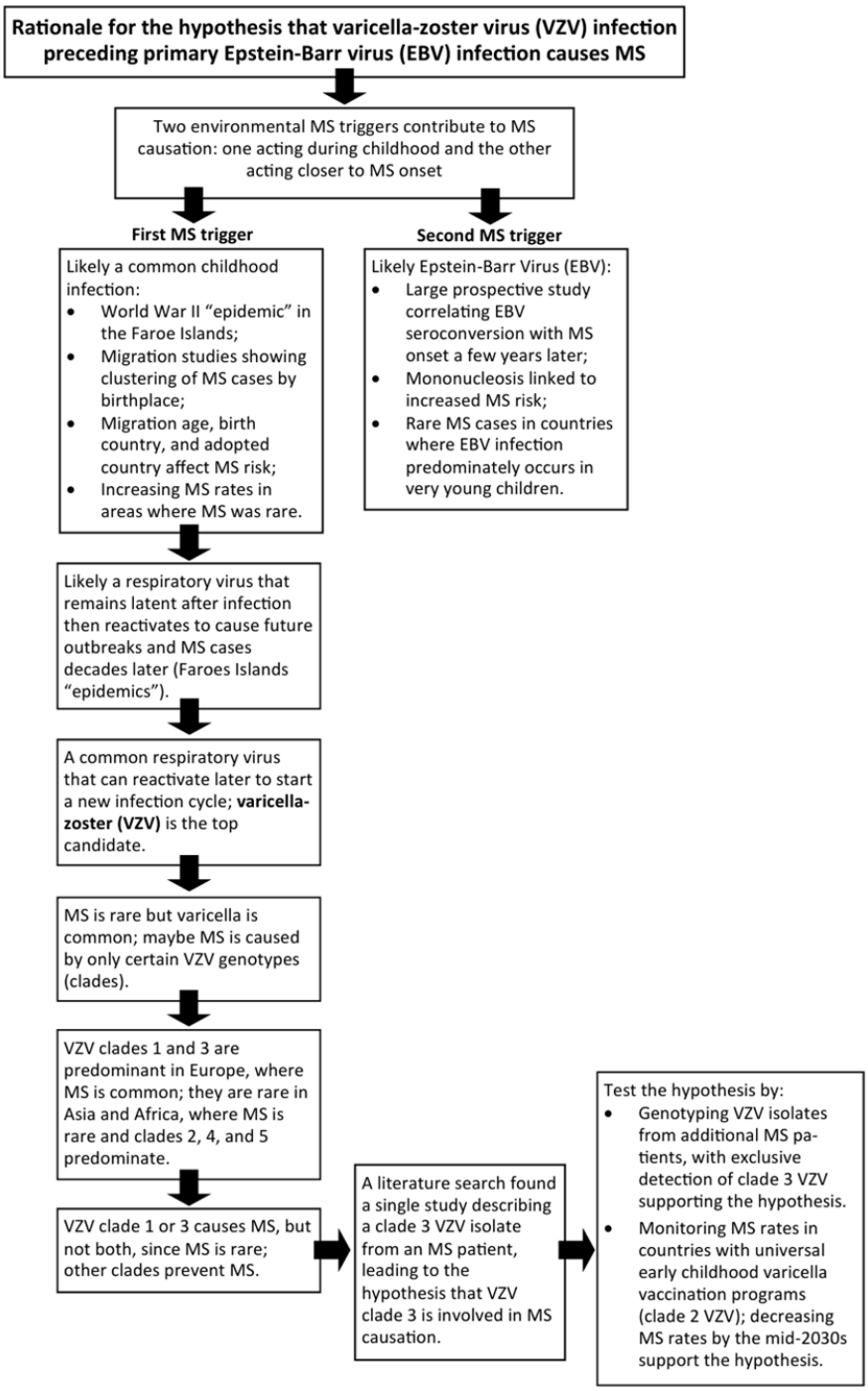

Figure 1. Flowchart illustrating the stepwise rationale for formulating the hypothesis

2.1. Evidence for EBV as the Second MS Trigger

Epstein-Barr virus (EBV) infection, which is usually asymptomatic in children, often leads to infectious mononucleosis (IM) in adolescents and adults, an illness that has been linked to MS. However, although over 95% of the global population is infected with EBV by age 50 [4-6], MS remains rare, affecting less than 0.04% of people worldwide [1], suggesting that EBV infection alone is not sufficient to cause MS [4]. Nevertheless, recent studies indicate that MS risk

significantly increases after primary EBV infection. For example, a pivotal study analyzing biennial blood samples from 10 million U.S. military recruits reported that 97% of initially EBV-seronegative individuals who later developed MS became seropositive approximately 2 to 15 years before disease onset, compared to a seroconversion rate of only 57% among those who did not develop MS [5]. Similarly, nearly all German patients with early-stage MS were EBV-seropositive, unlike their healthy counterparts [6].

Rates of delayed EBV infection differ greatly between populations, ranging from approximately 50% in areas with high MS prevalence to less than 5% in regions with very low MS prevalence [1,4,7]. In Asia and Africa, where MS is relatively rare, primary EBV infection typically occurs before the age of five through salivary transmission within households or daycare settings. Conversely, countries with higher MS rates, such as the U.S. and northern European nations, feature higher primary EBV infection rates in adolescence or adulthood attributable to other forms of salivary transmission, such as kissing [1,4].

Despite substantial evidence linking delayed EBV infection to heightened MS risk, it is important to emphasize that EBV infection alone is not sufficient to cause the disease [4]. As noted earlier, at least two environmental factors are considered necessary for MS development: one acting during early childhood and the other during adolescence or adulthood [5,9,10]. While delayed EBV infection may serve as the second trigger, the identity of the first childhood trigger remains uncertain. However, several clues to its identity are discussed in the following sections.

2.2. Clues to the First MS Trigger

2.2.1. Evidence for a Childhood Environmental Factor as the First MS Trigger

Key insights into a possible childhood trigger for MS have emerged from migration studies showing how MS risk can vary based on migration age and residence locations before and after migration [4]. Young migrants tend to experience the most significant changes in MS risk, with the likelihood of MS development either increasing or decreasing depending on their new environment [4,11]. Generally, children who move from regions with high MS prevalence to areas with low prevalence see a reduction in MS risk, while those migrating in the opposite direction do not necessarily experience an increased risk [4].

A pivotal study found that immigrants moving to a country with very high MS prevalence (Denmark) from countries with low or moderate prevalence had a lower lifetime relative risk (RR) of developing MS than native Danes [11]. Importantly, RR was influenced by migration age: immigrants who relocated before age 15 exhibited higher MS risk than those moving after age 15. Interestingly, MS rates in second-generation immigrants were intermediate between those of their parents and native Danes, suggesting a partial transfer of protective environmental factors to the younger generation after migration from lower-risk regions.

Another clue comes from the documented but debated MS outbreaks occurring between 1940 and 1999 involving 21, 10, 10, and 13 cases on the Faroe Islands, a territory of Denmark [4,12], which began during the British occupation of these 18 remote North Atlantic islands involving thousands of troops during World War II (WWII). The first outbreak featured a rapid rise in MS incidence from 0 in 1941 to over 10 MS cases per year in 1945 and 1946, resembling a type I epidemic. Residences of MS cases were closely aligned with troop encampment locations across the islands, where troop numbers ranged from 1,500 to over 7,000 during the war, who regularly interacted with the 27,000 residents.

While the validity of the outbreaks has been questioned, no pre-war MS cases in Faroese residents were found in medical records reviewed after the war. The first outbreak of MS cases, with disease onset peaking in 1945, appeared to involve the widespread transmission of an agent from asymptomatic British troops to native Faroese, including some as young as 11 years old [12], a pattern inconsistent with EBV transmission (via saliva), but suggestive of a highly contagious agent spread through the respiratory route. Further peaks in MS incidence approximately every 15 years through the 1990s suggest that the unidentified agent may have established latency and undergone periodic reactivation, a characteristic observed in herpesviruses and retroviruses. While most of these viruses are transmitted through intimate contact involving the exchange of body fluids, the herpesvirus varicella-zoster virus (VZV) is an exception as an airborne pathogen—making it a compelling candidate for the initial trigger of MS.

2.2.2. Overview of VZV

VZV is a highly contagious pathogen transmitted mainly through close contact or inhalation of viral particles released from skin lesions or respiratory secretions of individuals with varicella (chickenpox) or shingles (zoster) [13]. Individuals recovering from varicella infection typically develop lifelong immunity to symptomatic reinfection, as indicated by the detection of serum antibodies against VZV antigens demonstrating VZV seropositivity or positive seroprevalence. However, after recovery from primary VZV infection, the virus remains latent in the host for life except when it reactivates, usually after age 50, causing shingles. This unique lifecycle allows VZV to persist in small, isolated populations, such as those in the Faroes, where decades-long latency in individuals with varicella (chickenpox) as children can result in viral reactivation as shingles (zoster). Reactivated virus from zoster lesions or respiratory secretions can then spread via airborne transmission, triggering new varicella outbreaks [13].

VZV strains are genetically diverse, consisting of several families or "clades" that circulate in different regions globally. Notably, the genotype of VZV found in a patient’s zoster lesions matches the genotype of VZV responsible for their original chickenpox infection, as initial infection confers lifelong immunity against symptomatic reinfection with other clades. Thus, genotyping VZV from zoster lesions of elderly native residents can offer insights into the clades of VZV that circulated during varicella outbreaks in a region decades earlier.

2.2.3. The Link Between Varicella and MS

Numerous studies have explored the association between VZV and MS, yielding conflicting results. Some research suggests that populations at polar latitudes experience higher rates of both childhood varicella and MS, implying a potential role for VZV in MS causation [14]. Conversely, other studies show that MS patients and age-matched controls in high-prevalence regions have similar VZV seroprevalence rates, indicating no direct correlation between VZV infection and MS risk [15]. However, in areas with high childhood varicella rates, the resulting high seroprevalence cannot exclude a potential link between VZV infection and MS, as seroprevalence data do not differentiate among VZV clades, some of which may be associated with MS. Thus, VZV genotyping studies are needed to clarify any varicella-MS connection.

One example comes from an epidemiological study of a Hutterite community in Manitoba, Canada, which found fewer MS cases compared to surrounding non-Hutterite populations with very high MS rates [16]. The study reported a lower varicella seroprevalence rate (72%) among Hutterites compared to a matched control group (90%), supporting the hypothesis that VZV infection may be a direct MS trigger. Given the presence of both high- and low-risk populations at the same latitude, these findings suggest that latitude may be only indirectly associated with

MS risk, possibly through its impact on climate, which influences varicella transmission efficiency, which is higher in temperate compared to tropical regions [13].

Additional support for the role of VZV as an MS trigger comes from several studies linking childhood VZV infection to an increased risk of MS. For example, both VZV and MS rates are rising in Mexico [17]. Additionally, VZV DNA has been detected in peripheral blood mononuclear cells (PBMCs) of MS patients during relapses but not during remission [18,19]. Moreover, in Iran, higher levels of VZV DNA have been found in PBMCs of MS patients compared to healthy controls, despite no significant differences in plasma VZV-specific antibody levels between the two groups [20]. Furthermore, in northern Jordan, where both varicella and MS are less common than in Europe and North America, higher anti-VZV seroprevalence rates have been observed in MS patients (98%) compared to controls (85%) [21]. This finding suggests that the VZV-MS association may be more detectable in populations with lower adult VZV seroprevalence rates, unlike in northern Europe and North America, where over 90% of pre-adolescent children are already seropositive [13].

Further evidence of a VZV-MS association is provided by a UK study, which found higher rates of past chickenpox and shingles events in MS patients compared to age-matched non-MS controls [22]. VZV has also been shown to infect oligodendrocytes, the primary cells targeted in MS [23]. Treatment with acyclovir, an antiviral used for shingles that inhibits viral replication but not reactivation, has been shown to reduce the rate of exacerbations in patients with relapsing-remitting MS [24].

Notably, universal childhood varicella vaccination has been practiced in the U.S. since 2006, in Japan since 2014, and in Canada and several northern European countries beginning in the early 2000s. Before a varicella vaccine became available, over 90% of individuals in temperate climates contracted chickenpox before adolescence, compared to significantly lower rates in tropical regions [13]. Interestingly, countries with high MS rates are predominantly found in temperate zones, suggesting a link between MS risk and VZV infection, despite similarly high VZV seroprevalence rates in both MS patients and controls [15]. However, VZV seroprevalence only indicates past infection with a diverse group of viruses, raising the possibility that MS may be linked to a specific VZV genotype prevalent in regions with high MS rates (e.g., northern Europe, North America) but less common in areas where MS is rare (e.g., Africa, Asia).

2.2.4. Evidence for Clade 3 VZV as the First MS Trigger

Varicella is caused by the herpesvirus VZV, classified into five main genotypic groups or clades (1-5) that generally circulate in distinct geographical regions [25,26]. Clades 1 and 3 are predominantly found in Europe and regions historically colonized by Europeans, such as the United States, Canada, and Australia [25], where MS prevalence rates are notably high. In contrast, clades 2, 4, and 5 are more common in Asia and Africa, areas with much lower MS rates [1].

Notably, clade 2 VZV infection is unlikely to be an MS trigger, since Japan has historically had low MS rates (under 20 cases per 100,000 population) despite high pre-vaccine-era childhood varicella rates caused by clade 2 VZV infection [27,28]. However, a 2019 study reported that VZV belonging to an unidentified European clade was found in 1 of 50 Japanese varicella cases [28], indicating recent entry of either clade 1, 3, or both clades into Japan. If the hypothesis is correct, this introduction of European VZV clades may partly explain the observed increase in MS rates in northern Japan, where MS prevalence doubled from 8.1 cases per 100,000 people in 2001 to 16.2 per 100,000 in 2011 [29], suggesting the need for further research.

While rising MS rates in Japan may partly result from improved diagnostic practices, the increase in delayed EBV infection rates could also be a contributing factor. This is supported by a study showing that the primary EBV infection rate among 5-7-year-old Japanese children dropped from over 90% in 1975 to 59% in 1995-1999 [30], a range similar to the 55%-70% seroprevalence rates observed in the U.S. and Germany, countries with approximately 19 times higher MS prevalence (~300 cases per 100,000 persons) [1,7]. Therefore, differences in delayed EBV infection rates alone do not fully account for disparities in MS prevalence between Japan and countries with significantly higher MS rates, necessitating consideration of additional factors when exploring the relative rarity of MS in Japan. Such factors include variations in EBV strains, low genetic susceptibility and/or increased resistance to environmental MS triggers [31], potential underdiagnosis of MS, and differences in circulating VZV clade distributions between Japan and regions with higher MS prevalence.

The high prevalence of MS in European countries, where VZV clades 1 and 3 are predominant, suggests a potential association between these clades and increased MS risk. This is supported by a study reporting VZV genotyping data from a single MS patient with shingles between 2003 and 2007, whose lesions contained clade 3 VZV (genotype D) [32]. The 75-year-old patient likely contracted chickenpox 60-70 years earlier, in the 1930s or 1940s. Although no additional VZV genotyping data from other MS patients were found, this case provides preliminary evidence supporting the hypothesis that childhood infection with clade 3 VZV may contribute to MS development, highlighting the need for further investigation.

Interestingly, the aforementioned study identified 25 clade 1 and 20 clade 3 VZV isolates from individuals aged 1–86 years between 2003 and 2007, indicating widespread circulation of these clades in Europe since at least the 1920s. A separate study in East London, England, found that individuals who had chickenpox before 1920 were primarily infected with clade 1 VZV, while clade 3 circulated at significant levels after 1930, accompanied by low levels of clades 2 and 5 [33]. Moreover, a 2013 study revealed that although clade 1 remained prevalent across Europe, it faced significant competition from clades 3 and 5 [34]. These findings suggest a long-standing presence of clades 1 and 3 in Europe, a region with high MS prevalence, underscoring their potential role in MS causation. Furthermore, the observed shifts in VZV clade distributions due to changing migration patterns may have global implications for MS risk if clade 3 VZV is a significant risk factor.

2.2.5. Did Clade 3 VZV Contribute to the Putative WWII Faroes MS Outbreak?

Given that Kurtzke et al.'s studies in the Faroe Islands were pivotal in shaping the hypothesis that viral infections significantly contribute to MS causation, does this hypothesis align with the suspected MS outbreak in the Faroes? Varicella cases on the islands averaged 138 per year between 1934 and 1939, rising to 211 cases annually between 1940 and 1945 [35, supporting information], likely due to VZV clades 1 and/or 3. If clade 1 was the dominant strain before WWII, it is plausible that British troops stationed in the Faroes in 1940 introduced clade 3, spreading it to the local population during their occupation from 1940 to 1945. However, no widespread chickenpox outbreaks or shingles cases were reported among the troops [12].

Reports of asymptomatic VZV shedding by astronauts under stress [36] and by immunocompetent children hospitalized for prolonged fever who had previously experienced varicella infection but not varicella vaccination [37] suggest that clade 3 VZV could have been transmitted asymptomatically from British troops to the Faroese population, warranting further investigation. Moreover, VZV clade 1 and 3 genotypes have been detected in shingles patients in Iceland, another North Atlantic territory under British control during WWII, where a putative post-war spike in MS cases was also noted [38]. These patients likely contracted chickenpox

between the 1930s and 1960s [25], emphasizing the importance of genotyping VZV from native Icelandic and Faroese patients who had varicella before, during, and after the war to understand VZV circulation patterns as they relate to MS incidence.

Furthermore, individuals who had chickenpox long ago may harbor infectious VZV in their saliva [36], theoretically transmitting the virus via coughing or sneezing. Subclinical reinfections of immunocompetent individuals with wild-type VZV have been documented [37,39-41], including a case involving a 30-year-old man who developed herpes zoster caused by clade 5 VZV and experienced a second episode of zoster caused by clade 3 VZV four years later. These wild-type VZV reinfections may be more common than previously believed [41] and have even been reported in individuals vaccinated with the OKA varicella vaccine [40]. Consequently, the hypothesis that clade 3 VZV was asymptomatically transmitted from British troops to native Faroese during WWII remains plausible and merits further exploration.

2.3. The Hypothesis and its Alignment with MS Epidemiological Features

The hypothesis, which suggests that MS is triggered by clade 3 VZV infection preceding primary EBV infection, can be further tested by examining its alignment with established MS epidemiological patterns. The following sections will explore the ability of the hypothesis to account for the 20th-century latitude gradients in Europe and North America and their recent attenuation in some places, shifting geographic distributions of VZV clades, rising female-to-male MS ratios, increasing MS rates among African Americans, differing MS prevalence between migrants and non-migrants, rising MS incidence in certain countries, and exceptionally high MS rates in Sardinia, Italy.

2.3.1. Alignment with 20th-Century Latitude Gradients of MS Prevalence

During the 20th century, significant north-to-south gradients in MS prevalence were documented in North America and Europe, often attributed to the geographic distribution of populations with high genetic susceptibility to MS and differences in ultraviolet light exposure, as well as global climatic features associated with latitude. Temperate climates, typically found at higher latitudes, tend to have higher MS rates, while tropical climates, found at lower latitudes, have lower MS rates, due to climate-associated differences in VZV transmission efficiency and the age of primary infection [13-15]. In temperate climates, approximately 90% of people are infected with VZV during childhood, whereas in tropical regions, VZV infections more commonly occur during adolescence or adulthood [13].

However, this pattern does not apply to Japan—a temperate country with high childhood varicella rates [27] but very low MS prevalence of <20 cases per 100,000 population [1]. This anomaly, however, may support the hypothesis, as over 98% of varicella cases in Japan before the varicella vaccine rollout were caused by clade 2 VZV [28], unlike European clades 1 and 3, which are more prevalent in regions with higher MS rates [25,26,34,42].

If clade 3 VZV contributes to MS risk, its prevalence should align with the 20th-century latitude gradients of MS prevalence. This seems to be the case, as clade 3 VZV has been reported to be most prevalent in northern European countries with very high MS rates, such as Iceland, Finland, and Germany [1,25,26]. Nevertheless, further VZV genotyping studies similar to the study conducted in East London, UK [33] are needed to provide comprehensive snapshots of VZV genotypes circulating during chickenpox epidemics across the U.S. and Europe throughout the 20th century.

Alternatively, the observed MS latitude gradient may align with latitude-based variations in adolescent or adult EBV infection rates [7] or the distribution of different EBV strains across latitudes [4, 43-46]. Additionally, the combined effects of clade 3 VZV and/or EBV on MS causation may be more pronounced at higher latitudes, as indicated by earlier MS onset in these regions [47]. However, the strength of MS latitude gradients may be shifting, presenting another opportunity to test the proposed hypothesis, as discussed in the next section.

2.3.2. Shifting VZV Clade Distributions and MS Latitude Gradients

In recent decades, the previously noted MS prevalence gradients have been diminishing in some regions while strengthening in others [47,48]. Given that VZV is carried exclusively by humans, changes in VZV clade distributions may reflect human population movements. If clade 3 VZV plays a role in MS risk, alterations in MS gradients could be partly due to the migration of populations carrying clade 3 VZV. Such shifts in viral genotypes have been observed in East London, an area with a large immigrant population, where clades 3 and 5 gradually increased in prevalence from the 1930s to the 1990s [33] and continued to circulate in the early 2000s [25,34]. These changing distributions may also explain the rising MS incidence rates in Japan, where one or both European VZV clades circulate [28], and in Mexico, where the circulation of both clades 1 and 3 has been noted (referred to as E1 and E2, respectively [49]). Therefore, the movement of VZV clade 3 in recent decades may be associated with diminishing MS latitude gradients in the U.S. and Europe and increasing MS rates in Japan and Mexico, warranting further study.

Given that the circulation of multiple clades in a population leads to inter-clade competition for hosts, introducing non-clade 3 VZV strains into regions where clade 3 predominates could reduce clade 3 infection rates. This, in turn, might result in lower MS incidence decades later when the exposed individuals reach the peak age of MS onset (around 30 years). Thus, if the proposed hypothesis is correct, MS rates would be lower in regions with significant inter-clade competition compared to those with predominant clade 3 circulation. Similarly, regions with universal early childhood varicella vaccination programs (clade 2 VZV) might experience declining MS incidence, contributing to the attenuation of MS latitude gradients.

In the early 21st century, the U.S., Japan, and several European nations introduced mandatory early childhood VZV vaccination, significantly reducing varicella incidence [50]. If clade 3 VZV plays a role in MS causation, administering the clade 2 OKA vaccine could attenuate the latitude gradient by lowering MS rates in vaccinated countries, which are often located at latitudes with the highest MS rates. This effect might become evident by the mid-2030s, as individuals who received the two-dose varicella vaccine (introduced in 2006) approach their late 20s and early 30s when MS incidence peaks [1]. Additionally, if varicella vaccination helps prevent MS, pediatric MS rates should already be declining in vaccinated populations. However, no large-scale studies have yet demonstrated these trends.

If the hypothesis is correct, population movements, such as immigration or troop deployment, could be altering the global varicella clade distribution. For example, the introduction of clade 3 VZV into regions with low MS rates may result in increased MS rates decades later. Conversely, migrations from low-MS regions to high-MS regions may introduce MS-protective clades (e.g., clades 2, 4, and 5), leading to inter-clade competition and potentially reducing MS rates over time. Additionally, modernization, characterized by improved hygiene and smaller family sizes, may increase delayed primary EBV infection, which raises the likelihood of varicella preceding EBV infection, thereby heightening MS risk in areas where clade 3 VZV predominates. Ultimately, these factors could lead to higher MS rates in regions where MS was previously rare, such as tropical areas, and lower rates in historically high-MS regions, potentially diminishing the latitude gradient in certain areas [48].

2.3.3. Can the Hypothesis Explain Increasing Female-to-Male MS Ratios Since WWII?

During the 1940s, the ratio of female to male MS cases in both northern and southern Europe was approximately 2:1. However, by the late 1980s, this ratio had increased to nearly 4:1 in some areas of northern Europe, while remaining at 2:1 in southern Europe [51]. Although it is challenging to attribute these changes directly to sex-based differences in exposure to clade 3 VZV versus other clades, there could be a link between these shifts and differences in the timing of VZV and primary EBV infections, particularly in women.

A study conducted in England and Wales before the introduction of the varicella vaccine showed notable sex-based differences in the incidence rates of chickenpox and shingles. The study found higher chickenpox rates among females aged 15-24 compared to males in the same age group, while equivalent shingles rates were observed between the sexes [52]. In other age groups, female shingles rates exceeded those of males. Additionally, German data indicated that although boys and girls had similar EBV seroprevalence rates, adult males had significantly lower EBV seroprevalence and serum EBV-specific antibody titers than adult females [53]. The authors attributed this result not to a lack of prior exposure to the virus in males but to their less robust antibody response to EBV, potentially due to a stronger cell-mediated response that prevents EBV reactivation and reduces the boosting of an anti-EBV humoral response. These results suggest that female status is an MS risk factor, as males may suppress EBV reactivation more effectively than females following primary infection after puberty. Hormonal differences between the sexes may contribute to a higher MS risk in women. However, further studies are needed to determine whether the seronegative adult males in the study were never infected with EBV or simply did not generate a strong humoral response.

A study in Denmark reported that the incidence of MS in women aged 60 and younger more than doubled between 1950 and 2009, increasing from approximately 6 to 12 cases per 100,000 population per year, with the most pronounced rise observed in women over 50, while men experienced only a modest increase [54]. These changes are unlikely to be attributed to known MS risk factors such as obesity and smoking but may be linked to delayed age at first pregnancy and fewer births overall, warranting further investigation. This trend could support the hypothesis if more women contract primary EBV infection later in life due to the postponement of dating or marriage for educational or professional reasons.

Alternatively, the increasing female-to-male MS ratio may reflect differences in post-pubertal EBV infection dynamics driven by distinct behavioral patterns between the sexes, as emphasized in another Danish study. In this context, girls tend to reach puberty earlier than boys and often date older boys, while boys initially date younger girls [55]. Notably, girls who contract primary EBV shortly after puberty experience sharply rising IM rates, suggesting that hormonal influences on the immune response to primary EBV infection may differ significantly between the sexes, predisposing females to higher rates of IM and potentially contributing to the growing female-to-male MS ratio. Given that most Danes likely contract varicella before adolescence, similar to other northern European countries, these sex-based differences in MS rates appear to be more closely linked to the effects of sex hormones on the second MS trigger: primary EBV infection.

The human relationship with herpesviruses has evolved over the 20th century due to various lifestyle changes. For example, the replacement of breastfeeding with bottle feeding has reduced cytomegalovirus (CMV) infection rates [56], while improved hygiene practices and smaller family sizes [54] have increased delayed EBV infection and IM rates [57]. Concurrently, the increased enrollment of children in daycare facilities has led to higher rates of early VZV infection [58]. These combined changes may have disproportionately impacted female MS

susceptibility compared to males, potentially contributing to rising female-to-male MS ratios since WWII.

2.3.4. Can the Hypothesis Explain Increasing MS Incidence in African Americans?

A comprehensive study comparing MS incidence among African American and White U.S. soldiers across different conflicts, including the Gulf War, Vietnam War, and WWII, revealed intriguing trends. During WWII, the MS incidence rate was lower for African Americans than for White soldiers. However, over the subsequent decades, the rate among African Americans gradually increased, eventually surpassing that of Whites by 2013 [59].

This trend may support the proposed hypothesis, as lower EBV seroprevalence rates were observed in preadolescent African American children (aged 9-11) between 2009-2010 compared to those in 2003-2004 [60]. Alternatively, the increased mixing of different ethnic groups in recent years might have facilitated the transmission of clade 3 VZV from White populations of northern European descent to African Americans, though current VZV genotyping data from the U.S. are insufficient to confirm this hypothesis.

Another possibility is that historical underreporting of MS in non-White populations could have contributed to the observed increase in reported MS rates among African Americans [61]. However, further research is needed to determine whether this factor fully explains the trend.

2.3.5. Does the Hypothesis Explain Different MS Rates in Migrants versus Non-Migrants?

Studies on MS risk in migrant populations have provided valuable insights into potential disease-causing factors by showing that future MS risk is influenced by MS prevalence rates in both the country of origin and the adopted country [4], and migration age [4,11,62,63]. Migrants moving from areas with low MS prevalence to regions with high prevalence are generally protected from developing MS, while reverse migration offers varying degrees of protection depending on the age at migration and other factors. Interestingly, second-generation children born to migrants from low-prevalence areas who relocate to high-prevalence regions may have a higher risk of developing MS than their first-generation immigrant parents, and in some cases, their risk may even exceed that of natives in the adopted country [11,63]. These findings suggest the existence of protective factors in low-prevalence areas that counteract the effects of later exposure to MS-triggering agents.

In the context of the proposed hypothesis, two scenarios involving migrants moving between high and low MS prevalence areas can help elucidate the effects of migration on childhood VZV clade 3 and EBV infection rates. In the first scenario, migrants moving at very young ages from low-prevalence regions (e.g., Japan, Africa) to high-prevalence areas may retain protection against MS due to high early childhood EBV infection rates in their original locations [7], increasing the likelihood that they contract primary EBV before exposure to VZV clade 3 or other clades. Additionally, in their birth countries, these migrants may have been exposed to non-European VZV clades, such as clades 2 or 5, which could potentially offer protection from MS if the disease is triggered by clade 3 VZV.

In the second scenario, migrants moving from high-prevalence to low-prevalence regions are less likely to be protected from developing MS compared to those in the first scenario. This is because they are likely to contract clade 1 or 3 VZV during childhood, possibly through exposure in daycare or elementary school settings [64] unless they migrate at a very young age. Furthermore, depending on their ethnicity and socioeconomic status [7], a substantial proportion may not acquire EBV until after childhood, as EBV infection tends to be delayed in populations with high

MS prevalence. Consequently, many migrants relocating from regions with high to low MS prevalence may experience childhood exposure to clade 3 VZV in their birth country (depending on their home country and age of migration [34,62,63]) before encountering EBV in adolescence or adulthood in their adopted country, thus retaining a higher MS risk regardless of migration age.

2.3.6. Can the Hypothesis Explain Rising MS Incidence in Some Countries?

Rising MS incidence rates have been reported in various countries throughout the latter half of the 20th century, though some of these increases may be attributed to improved case ascertainment and greater access to medical care [1]. However, a comprehensive retrospective study in Denmark, a country with high MS incidence, excellent healthcare infrastructure, accurate case identification, and no universal varicella vaccination program, documented more than doubling of MS rates among women between 1950 and 2010, with only modest increases among men [54]. Similarly, rising MS incidence rates have been observed in Japan [29], potentially due to the increased circulation of European VZV clades [28], and in Mexico [17], where both clades 1 and 3 circulate (referred to as E1 and E2, respectively) [49].

These trends could be explained if clade 3 VZV infection rates and/or delayed primary EBV infection have increased, or if the timing of varicella onset has shifted earlier while EBV infection occurs later in recent decades. A 2019 Danish study reported relatively low EBV seroprevalence (around 41%) among 10-year-olds, suggesting that delayed EBV infection rates may have risen [55], as previously observed in Japan [30]. However, no data are currently available on historical EBV seroprevalence or VZV genotypes in Denmark. Given that VZV seroprevalence among 10-year-olds is likely high in Denmark, as in other northern European countries [64], it is plausible that the rising MS rates may be linked to increased clade 3 VZV infection, delayed EBV infection, or both—warranting further investigation. These factors are further explored in the next section, which addresses high MS rates in Sardinia and rising MS rates across Italy in recent decades.

2.3.7. Can the Hypothesis Explain the Extremely High MS Rate in Sardinia, Italy?

MS prevalence in Sardinia, Italy, a southern European island (Figure 2) with a culturally distinct, genetically stable population, ranks among the highest worldwide, with 330 cases per 100,000 people [2], defying the 20th-century latitude gradient rule. MS prevalence rates there range from 217 cases per 100,000 population in the Olbia-Tempio district in eastern Sassari Province, to 425 cases per 100,000 in the Ogliastra district of Nuoro Province.

Figure 2. Map of Italy with a magnified drawing of Sardinia. Sardinia (orange) contains five provinces and the region with the highest MS rate, the Ogliastra region of Nuoro Province, shown in red (adapted from map provided courtesy of Vonvikken, Public domain, via Wikimedia Commons, https://commons.wikimedia.org/wiki/File:Map_of_province_of_Ogliastra_(region_Sardinia,_Italy)_(2001%E2%80%932016).svg).

If the hypothesis is correct, the extraordinarily high MS rate in Sardinia could be due to a combination of high early childhood clade 3 VZV infection rates and high rates of delayed EBV infection. Although data on these risk factors in Sardinia are limited, a 2013 study reported a notably lower EBV seropositivity rate of just 69% among healthy middle-aged Sardinians [65] compared to overall adult rates exceeding 90% in other regions of Italy and elsewhere [66,67]. Additionally, an exceptionally high clade 3 VZV infection rate (~80%) was observed in varicella patients on the nearby island of Sicily in the early 2000s [34]. These findings suggest that the unique MS rates in Sardinia may result from the combined effects of both proposed risk factors, requiring further investigation.

Studies conducted during the second half of the 20th century suggest that MS risk in Sardinians was not always high but began to rise significantly by the 1970s, continuing unabated to 2020 following a semi-parabolic curve [68]. Intriguingly, a pivotal 2001 study in Nuoro Province highlighted a significant shift in the impact of emerging unidentified environmental factors, rather than genetic changes, on lifetime MS risk between residents born before and after 1946, marking the end of WWII as a critical period when MS risk began to increase [69]. Meanwhile, additional studies in Sardinia found a strong link between MS risk and birth year, implying that early childhood environmental factors shape MS risk [10,70].

Given that MS onset typically peaks between ages 20 and 40, these unknown risk factors potentially emerged decades before MS rates across Sardinia began to surge in the 1970s, when Sardinians born after 1946 first reached their 20s and 30s, the peak age range of MS onset. Rising MS incidence and prevalence rates after the early 1970s through the 21st century have also been reported in the southern Italian island of Sicily and in northern Italy [68], suggesting that the influence of these unidentified environmental factors on MS risk extends beyond Sardinia across Italy. Furthermore, spatial variability in MS rates noted in these studies [2,68] indicates their impact on MS risk can fluctuate dramatically even between adjacent regions.

For example, a 2016 Sardinian study found that the highest MS prevalence rate in sparsely populated Nuoro Province (419 cases per 100,000 people) was significantly higher than the lowest rate found in the adjacent area, the eastern half of Sassari Province (217 cases/100,000) [2]. Substantial MS prevalence differences between adjacent regions have also been reported in the Padan Plain in northern Italy, central Italy, and Sicily [68], underscoring the roles of shifting environmental factors on MS risk and supporting the hypothesis that infectious agents influence MS risk.

If the hypothesis is correct, surging MS rates in Italy may be due to an increased rate of delayed EBV infection, a higher incidence of clade 3 VZV infection, unusually early VZV infection, and/or unusually late primary EBV infection. Moreover, the exceptionally high MS rate in Nuoro Province, Sardinia may be a consequence of the pronounced effects of these contributing factors stemming from the region's extreme isolation and unique cultural norms. Specifically, a high rate of significantly delayed primary EBV infection, combined with potentially elevated levels of clade 3 VZV circulation in the province, may increase the likelihood that primary EBV infection occurs after clade 3 VZV infection, even in adults, potentially explaining why MS rates in the region are among the highest in the world.

2.4. Experimental Testing of the Hypothesis

The most direct approach for testing the hypothesis would involve genotyping VZV from biological samples collected from shingles patients, such as zoster lesions [32,71], saliva [34,72], or throat swabs [73]. One such method was successfully used to identify clade 3 VZV in the only MS patient for whom VZV genotyping data is available [32]. If genotyping reveals only clade 3 VZV in MS patient specimens, this would lend support to the hypothesis.

However, since 2006, many MS patients have received shingles vaccines containing the clade 2 VZV OKA strain before starting immunomodulatory treatments, protecting them from shingles. Without zoster lesions, obtaining VZV specimens is challenging because latent VZV exists at extremely low levels in cells and body fluids. Despite this, it may still be possible to amplify VZV DNA from other sources, such as white blood cells from elderly MS patients [74] or relapsing MS patients [18,19], saliva from MS patients receiving fingolimod treatment [75], or saliva samples from patients under stress [36]. Importantly, individuals vaccinated with the OKA strain harbor both the vaccine (clade 2) and wild-type VZV DNA from earlier varicella infections.

If clade 3 VZV is confirmed as the initial MS trigger, the sequence of VZV followed by EBV infection could be verified through extensive monitoring of varicella and EBV seroprevalence rates in countries with low varicella incidence, no varicella vaccination programs, and rising MS rates to correlate seroprevalence profiles with MS onset. Alternatively, examining MS trends in Sicily, where 70% of children born in 2005 received a single-dose varicella vaccine [76], and in other countries with vaccination programs since the early 2000s [77], could be conducted to monitor changes in MS rates, with decreasing MS rates by 2035 in these regions aligning with the hypothesis.

3. CONCLUSIONS

This study proposes that MS in genetically predisposed individuals results from two herpesvirus infections: infection with clade 3 VZV (as suggested by a single VZV isolate from an MS patient) followed by delayed EBV infection. If correct, universal varicella vaccination could help

prevent MS, while antiviral drugs that inhibit the reactivation of latent VZV and EBV infections might slow disease progression in MS patients.

The most direct way to test this hypothesis would be to determine if the VZV isolates from MS patients are exclusively clade 3. Should this link be confirmed, further investigations should explore whether the specific sequence of VZV and EBV infections influences MS risk.

In the meantime, monitoring adult and pediatric MS rates in countries with varicella vaccination programs [76,77] may reveal that the clade 2 OKA vaccine offers protection against MS. If so, countries without varicella vaccination programs, especially those with high MS incidence, might consider adopting such measures for MS prevention. Furthermore, if primary EBV infection occurring after clade 3 VZV infection triggers MS, this knowledge could guide the development of EBV vaccination protocols currently in the planning stages.

For much of human history, herpesviruses have coexisted with us, but recent lifestyle changes and increased migration may be altering our relationship with these viruses in ways that have unintended consequences. The order of VZV, EBV, and other herpesvirus infections, such as CMV, human herpesvirus (HHV)-6, HHV-7, HHV-8, and herpes simplex virus (HSV) 1 and 2 may play a vital role in supporting human health. Understanding these dynamics could help prevent dysregulated viral gene expression in human hosts and reduce the risk of MS and other autoimmune diseases.

To further investigate these possibilities, future studies should focus on large-scale genotyping of VZV from additional MS patients, comprehensive epidemiological monitoring in vaccinated versus unvaccinated populations, and exploring the effects of lifestyle changes on herpesvirus transmission dynamics. Such studies could provide clearer evidence regarding the potential role of VZV and EBV in MS, while potentially revealing new strategies for preventing and managing this debilitating disease.

An earlier version of this paper was presented at the 2024 International Conference in Life Sciences (LiSci2024) on September 14, 2024 [78].

ACKNOWLEDGEMENTS

The author would like to thank all of the researchers who have investigated the cause of MS. She would also like to thank her husband Nelson and sister Caree Updyke for their help in proofreading early drafts of the manuscript. This paper is dedicated to the author’s sister Carol, who suffered from MS for over 20 years.

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