VARICELLA VACCINATION AS A POTENTIAL MULTIPLE SCLEROSIS PREVENTION STRATEGY

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ABSTRACT

Multiple sclerosis (MS), a chronic, debilitating central nervous system disease afflicting over 2.8 million people worldwide, is caused by unknown genetic and environmental factors, including delayed Epstein-Barr virus (EBV) infection. Here a hypothesis is proposed whereby MS is caused by primary EBV infection contracted after clade 3 varicella-zoster virus (VZV) infection. The hypothesis aligns with MS risk factors (latitude gradients, changing prevalence, sex ratios, migration factors, and viral antibody seroprevalence rates). The proposed hypothesis, which is rooted in the detection of VZV clade 3 DNA in a single MS patient, requires confirmation through examination of a greater number of MS patient VZV isolates. If correct, declining MS incidence rates should be observed within the next decade in countries that began universal early childhood varicella vaccination programs in the early 2000s. Implications for unvaccinated populations with rising MS rates are discussed to highlight varicella vaccination as a potential MS prevention strategy.

KEYWORDS

Multiple Sclerosis, Varicella Vaccination, Epstein-Barr Virus, Varicella-Zoster Virus

1. INTRODUCTION

Multiple sclerosis (MS) is a complex, degenerative central nervous system (CNS) disease that exclusively affects humans. Despite more than 150 years of research, its exact cause remains unknown but is widely believed to result from interacting genetic and environmental factors that initiate a pathological process leading to the destruction of CNS myelin. MS primarily affects individuals during their prime reproductive years (ages 20-45 yrs.), although pediatric and late-onset MS cases have been reported. The disease initially presents with variable symptoms such as vision disturbances, muscle weakness, fatigue, and/or tingling sensations. Once triggered, MS manifests as a relapsing-remitting and/or progressively worsening disease, ultimately leading to the loss of voluntary and involuntary control over movement and bodily functions, significantly reducing the quality of life.

Globally, approximately 2.8 million people live with MS, with the highest incidence and prevalence observed in northern Europe, the United States (U.S.), Canada [1], and Sardinia [2]. While genetic factors account for about 25-30% of MS risk, concordance rates in identical twins [3] suggest that other factors are involved. Recent changes in MS incidence and prevalence rates offer critical clues to these environmental triggers, particularly in regions with rapidly rising MS rates. However, these apparent increases may partially reflect improved detection and diagnostic practices [1].

A comprehensive hypothesis explaining the cause of MS must account for several key observations: MS is a rare disease affecting approximately 1 in 300 people in high-risk areas and

1 in 3000 people globally [1]. It specifically targets the human CNS, with global prevalence rates ranging from 0 to 330 cases per 100,000 population [1]. MS onset predominantly occurs between ages 20 and 50 [1], and its prevalence exhibits significant geographical and ethnic variability. For example, MS is diagnosed more frequently in Caucasians than in Asians and Africans [1]. MS concordance in identical twins is at most only ~30%, highlighting a key role for environmental factors in disease causation [3]; Historically, MS incidence aligned with a latitude gradient, increasing from the equator to the poles, although this gradient may now be disappearing [1,4].

Epidemiological findings highlight other important factors that any hypothesis of MS causation must consider. The role of infection has been suggested [4], particularly given the reported MS epidemics in the Faroe Islands from 1940 through the 1990s and the unexpectedly high prevalence rates in Sardinia and southern Italy [4]. Migration studies indicate that MS risk is significantly influenced by age at migration and residence location before and after relocation [4]. Additionally, the female-to-male ratio of MS has shifted dramatically from 1:1 to over 4:1 in some areas over recent decades [1,4], and MS rates have increased among ethnic populations and in countries that were historically free of MS [1].

Studies have uncovered a strong link between Epstein-Barr virus (EBV) infection and MS, with previous EBV infection increasing MS risk by up to 32-fold [4-6]. Notably, MS is rare in regions where EBV infection occurs at a very young age [4,7], and a history of infectious mononucleosis (IM) during adolescence increases MS risk [8], although not all MS patients report a history of IM. Moreover, evidence points to at least two environmental triggers involved in MS development [4,5,9,10]. These findings highlight that a multifaceted approach is needed to uncovering the specific factors that initiate and drive MS pathogenesis.

2. TWO POTENTIAL ENVIRONMENTAL MS TRIGGERS

While the exact cause of MS remains unknown, extensive research has identified numerous genetic and environmental MS risk factors [1-4]. Notably, immigrant studies have shown that migrating from areas of low MS risk to areas of high MS risk does not change an individual's MS risk as much as migrating in the opposite direction [4], suggesting that environmental conditions during childhood influence adult MS risk. Furthermore, reports of temporal-spatial clustering of MS cases suggest that two MS triggers are required for MS development: one trigger acting at least 21 years before MS onset and the other acting just before disease onset [9], consistent with results of a Sardinian study [10]. Additionally, EBV infection has garnered abundant attention as a putative MS risk factor, due to compelling evidence linking delayed EBV infection occurring in adolescence or later to MS causation [4-6]. This study presents a hypothesis that MS is caused by two environmental triggers acting in a specific order: varicella caused by clade 3 varicella-zoster virus (VZV) followed by primary EBV infection. The rationale for the hypothesis is presented in the flowchart in Figure 1.

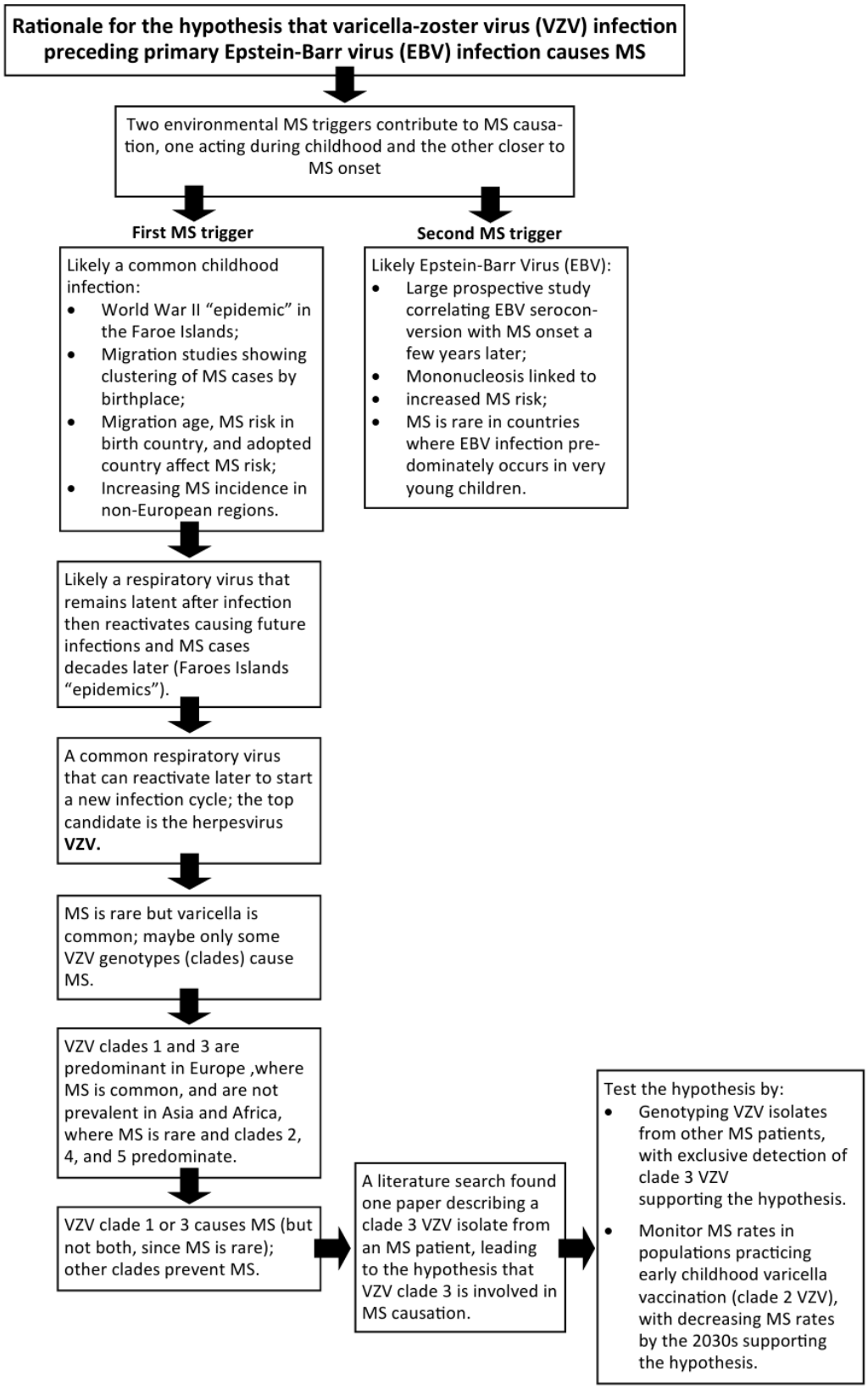

Figure 1. Flowchart illustrating the sequential development of the hypothesis.

2.1. EBV as the Second MS Trigger

EBV infection, generally asymptomatic in children, frequently causes IM in adolescents and adults which has been linked to MS [4,8]. However, EBV infects over 95% of people worldwide by age 50 [4-6], yet the overall prevalence of MS remains remarkably low, affecting less than 0.04% of the global population [1]. This disparity suggests that EBV infection does not always lead to the development of MS [4]. However, recent studies indicate that delayed primary EBV infection, defined here as occurring after age 11, significantly increases MS risk. For example, a large study of military recruits found that those who were EBV-seronegative at enlistment and later developed MS became seropositive before disease onset, whereas most matched controls who did not develop MS remained seronegative [5]. Similarly, German early-stage MS patients showed almost universal EBV seropositivity compared to controls [6].

Intriguingly, rates of delayed EBV infection vary significantly among populations, from approximately 50% in areas with high MS prevalence (~300/100,000) to <5% in regions with extremely low MS prevalence (<10/100,000) [1,4,7]. In Asia and Africa, where MS is relatively rare, primary EBV infection typically occurs before age 5 through salivary transmission within households or daycare settings. Conversely, in regions with higher MS rates, such as the U.S. and northern European countries, individuals are more likely to contract EBV during adolescence or adulthood through other modes of salivary transmission (e.g., kissing) [1,4].

Despite substantial evidence linking delayed EBV infection to increased MS risk, it is important to emphasize that EBV infection is not enough to trigger MS development [4]. As noted earlier, at least two environmental factors are believed to contribute to MS development: one acting during early childhood and another during adolescence or adulthood [5,9,10]. While delayed EBV infection may represent the second trigger, the identity of the first childhood MS trigger remains unknown, with clues to its identity discussed in the following sections.

2.2. Evidence that a Childhood Environmental Factor is the First MS Trigger

Several key clues relating to a childhood MS trigger have emerged from migration studies, shedding light on how MS risk can change depending on migration age and residence locations pre- and post-migration [4]. Importantly, younger migrants experience the most significant shifts in MS risk, with the likelihood of developing MS increasing or decreasing depending on their new place of residence [4,11]. Generally, children migrating from regions with high MS prevalence to those with low prevalence experience a reduction in MS risk, whereas MS risk does not necessarily increase for those moving in the opposite direction [4,11].

A critical study [11] demonstrated that immigrants moving from areas with low or medium MS prevalence to Denmark (a high-prevalence area) had a lower relative risk (RR) of developing MS during their lifetimes than native Danes, with RR values influenced by age of migration. Notably, immigrants who moved before age 15 to Denmark from areas with low or medium MS prevalence rates exhibited higher RR values than those who migrated after age 15. Interestingly, second-generation immigrants exhibited MS rates between that of Denmark and their parents' birthplaces, suggesting partial transfer of MS protection to the next generation due to unknown childhood environmental factors.

Another intriguing clue relates to the well-documented, yet controversial, Faroe Islands MS outbreak occurring during and after the World War II (WWII) British occupation of these isolated North Atlantic islands [4,12]. Although the outbreak's validity has been questioned, no Faroese MS cases predating WWII were discovered when researchers scoured medical records for MS cases after the war. Interestingly, the initial MS peak in 1941 exhibited characteristics

consistent with a geographically widespread epidemic involving the putative transmission of an MS agent from asymptomatic British troops to members of the native Faroese population, some as young as age 11 [12]. After the first infection peak, subsequent peaks in MS incidence were observed through the 1990s. Such features are inconsistent with the known mode of EBV transmission (salivary route) but instead align with characteristics of a highly contagious agent that is likely transmitted via the respiratory route. Furthermore, the apparent persistence of this agent in the Faroese population indicated it was a virus capable of establishing long-term latency in hosts before reactivating years later to initiate a new infection cycle, such as a herpesvirus or retrovirus. However, retroviruses are not generally associated with widespread epidemics, while the herpesvirus varicella-zoster virus (VZV), which is spread by the respiratory route, possesses these characteristics, Thus, VZV is the most likely first MS trigger.

2.2.1. Evidence for VZV as the First MS Trigger

VZV is a highly contagious virus primarily transmitted through close physical contact and/or inhalation of virus shed from skin lesions of infected individuals [13]. Primary VZV infection, commonly known as varicella or chickenpox, establishes lifelong latency and can reactivate decades later (usually after age 50) to cause shingles (zoster). This unique lifecycle enables VZV to persist even in small, isolated populations (e.g., the Faroe Islands). New infection cycles begin when uninfected individuals contract chickenpox by inhaling the virus in zoster skin lesions or respiratory secretions, subsequently spreading the virus to uninfected hosts via the respiratory route, triggering varicella outbreaks.

Importantly, VZV strains are genetically diverse and belong to several distinct families or "clades" circulating in various regions worldwide, as discussed below. Notably, the genotype of VZV found in the zoster skin lesions of a given patient matches that of the virus that caused chickenpox in the individual decades earlier, since varicella infection confers lifelong immunity against symptomatic infection with other clades. Consequently, genotyping of VZV in zoster skin lesions of natives in a geographic area can provide valuable insights into VZV genotypes that circulated during chickenpox epidemics in the same region many years before.

2.2.2. Evidence Linking VZV to MS

Numerous studies have explored the potential link between VZV and MS, yielding conflicting results. On the one hand, populations living at latitudes far from the equator exhibit higher childhood varicella rates and MS prevalence rates, suggesting that VZV may cause MS [14]. On the other hand, MS patients and age-matched controls in populations with high MS prevalence exhibit similar VZV seroprevalence rates, indicating that VZV infection is not directly correlated with MS risk [15]. However, seroprevalence rates cannot be used to rule out a role for VZV infection in MS, as several VZV subtypes (clades) exist that are not distinguishable based on seroprevalence data, necessitating genotyping studies to determine whether certain VZV clades or a single clade are etiologically linked to MS.

Further evidence for the role of varicella infection in MS causation can be found in an epidemiological study of a Hutterite population in Manitoba, Canada. MS is relatively rare among Hutterites living in the region, while surrounding non-Hutterite populations at the same northern latitude exhibit high MS prevalence rates [16]. Intriguingly, the study revealed that this Hutterite population had a lower varicella seroprevalence rate than the non-Hutterite Canadian age- and sex-matched control group (72% versus 90%, respectively), consistent with VZV infection as a direct MS trigger. Furthermore, these results imply that latitude is only indirectly correlated with MS risk. Putting it all together, the relationship between MS risk and latitude is consistent with the fact that latitude is directly associated with sunlight intensity and climate that,

in turn, influence childhood VZV infection risk [13], which is hypothesized here to increase subsequent MS risk.

Support for the role of VZV as an MS trigger can be found in other studies linking childhood VZV infection to increased MS risk. For instance, both VZV and MS rates are rising in Mexico [17]. Moreover, VZV DNA has been detected in PBMCs of MS patients during MS relapses but not during disease remission [18,19]. Additionally, higher quantities of VZV DNA have been found in peripheral blood mononuclear cells of Iranian MS patients compared to those of healthy controls in the absence of a significant intergroup difference in plasma VZV-specific antibody level [20]. Furthermore, in northern Jordan, where varicella and MS are both relatively less common than in Europe and North America, higher anti-VZV seroprevalence rates have been reported in MS patients (98%) versus controls (85%) [21], suggesting that it may be easier to detect a VZV-MS link in populations with lower adult VZV seroprevalence rates compared to populations in northern Europe and North America, where these rates exceed 90% before adolescence [13].

Additional evidence for a VZV-MS link is provided by a study conducted in the United Kingdom (UK), which revealed higher rates of previous chickenpox and zoster episodes in MS patients versus corresponding rates in age-matched non-MS controls [22]. Meanwhile, VZV has been reported to infect oligodendrocytes, cells specifically targeted by the MS disease process [23], while treatment of relapsing-remitting MS patients with acyclovir, a drug used to treat shingles, has been found to reduce the MS exacerbation rate [24].

Notably, universal childhood varicella vaccination has been implemented in the U.S. since 2006, in Japan since 2014, and in Canada and several northern European countries since the early 2000s. During the pre-vaccine era, over 90% of individuals living in regions with temperate climates contracted chickenpox before adolescence as compared to significantly lower childhood varicella rates in tropical countries [13]. Interestingly, countries with high MS rates are predominantly located in temperate zones, supporting a link between MS risk and VZV infection despite similarly high VZV seroprevalence rates in adult MS patients and controls [15]. Nonetheless, VZV seroprevalence is an indicator of past infection with a genetically diverse group of viruses, raising the question of whether MS is linked to a specific VZV genotype prevalent in regions where MS is common (Northern Europe, North America) but not in regions where MS is rare (Africa, Asia).

2.2.3. Evidence that a European VZV Clade is the First MS Trigger

Varicella is caused by a diverse group of viruses that are classified into five major VZV genotypic groups or clades (numbered 1-5), each with distinct geographical distributions [25,26]. Clades 1 and 3 predominate in Europe and regions historically colonized by Europeans (e.g., U.S., Australia [25]), where MS prevalence rates are notably high. By contrast, clades 2, 4, and 5 are predominantly found in Asia and Africa [26], regions with lower MS rates [1].

Importantly, clade 2 VZV infection is not likely an MS trigger, since MS rates in Japan have always been low, despite high pre-vaccine-era childhood varicella rates there of ~83% in 9-year-olds in the late 1980s [27] resulting predominantly from clade 2 VZV infection [28]. However, the dominance of clade 2 VZV in Japan may be diminishing, since a 2019 report noted that European VZV clades (clade 1 and 3) were isolated from 1 in 50 Japanese varicella cases [28]. This finding suggests that the recent introduction of European VZV clades to Japan may have contributed to the observed increase in MS rates in northern Japan, where the prevalence of MS doubled from 8.1 cases/100,000 persons in 2001 to 16.2 cases/100,000 persons in 2011 [29], warranting further study.

While increasing Japanese MS rates may be linked to improved MS diagnosis, increased delayed EBV infection rates (as mentioned above) may also be a contributing factor, as supported by a study showing that the primary EBV infection rate in 5-7-year-old Japanese children decreased from >90% in 1975 to 59% in 1995-1999 [30], within the range of rates between 55% and 70% observed in the U.S. and Germany, countries with approximately 20-fold higher MS prevalence rates (~300 cases/100,000 persons) [1,7]. Nevertheless, differences in delayed EBV infection rates alone do not fully explain the disparities in MS prevalence between Japan and countries with much higher MS rates. Thus, additional factors should be considered when investigating the relative rarity of MS in Japan, such as variations in EBV strains, low genetic susceptibility and/or higher resistance to environmental MS triggers [31], possible missed MS diagnoses, and different distributions of circulating VZV clades between Japan and countries with higher MS rates.

2.2.4. Evidence that Clade 3 VZV is the First MS Trigger

As mentioned above, MS is highly prevalent in European countries, where VZV clades 1 and 3 predominate, suggesting a potential association between these European VZV clades and increased MS risk. However, despite an extensive literature search for MS case reports describing VZV genotyping data, only one MS case with relevant genotyping information was found. This case involved an MS patient afflicted with shingles between 2003 and 2007 whose skin lesions contained clade 3 VZV (referred to as genotype D in the report) [32]. The patient, aged 75, likely contracted childhood varicella (chickenpox) approximately 60-70 years earlier, during the 1930s or late 1940s. Unfortunately, no additional VZV genotyping data for other MS patients were discovered, highlighting the need for further research. At present, this single case provides the only direct evidence supporting the hypothesis that childhood clade 3 VZV could be a potential trigger for MS.

Interestingly, VZV clades identified in the abovementioned study [32] included 25 clade 1 and 20 clade 3 VZV isolates obtained from 2003-2007 from subjects aged 1-86 years. These results indicate the widespread circulation of clades 1 and 3 in Europe since the 1920s or even earlier, aligning with other studies [25,26]. Similarly, another study of shingles patients in East London, England, indicated that those who had chickenpox before 1920 were infected with clade 1 VZV (referred to as genotype C) [33]. After 1930, clade 1 remained predominant in the area through the 1990s, despite the emergence and increasing prevalence of clades 2, 3, and 5 beginning in the 1930s (referred to as genotypes J, B, and A, respectively). Subsequently, a 2013 report of VZV genotypes associated with varicella cases indicated that although clade 1 continued to be isolated in East London, its predominance had been eclipsed by relative increases in proportions of clades 3 and 5, although only 36 samples were analyzed [34]. These findings demonstrate the longstanding predominance of clade 1 and clade 3 VZV in Europe, a region of high MS prevalence, highlighting the potential role of one or both of these clades in MS causation.

2.2.5. Evidence that Clade 3 VZV Triggered the Putative WWII Faroes MS Outbreak

Although varicella cases were reported in the Faroes before WWII (between 1934 and 1939), averaging 138.4 cases per year [35], they were likely caused by VZV clade 1 and/or clade 3. However, if clade 1 predominated there as it did in East London before WWII, it is plausible that British troops arriving on the islands beginning in April 1940 may have brought clade 3 VZV with them and transmitted it to the island population from 1940 until their departure in 1945 [12]. Interestingly, higher numbers of varicella cases were reported during the 1940-1944 British occupation, averaging 210.9 cases per year [35], consistent with this scenario, although this author found no information in the literature describing widespread chickenpox outbreaks or shingles cases among the soldiers. Nonetheless, reports of asymptomatic shedding of VZV by

astronauts under stress [36] and by hospitalized, immunocompetent children with histories of remote chickenpox (but not varicella vaccination) [37] indicate that asymptomatic transfer of clade 3 VZV from British troops to Faroese natives may have occurred, warranting further study.

Notably, VZV clade 1 and 3 genotypes have been detected in shingles patients in Iceland, another North-Atlantic Danish territory under British occupation during WWII with a putative post-war spike in MS cases [38]. These patients likely had chickenpox between the 1930s and 1960s [25], underscoring the value of genotyping VZV from native Icelandic and Faroese zoster patients who had varicella before, during, and after WWII in providing snapshots of VZV genotypes circulating there before, during, and after reported MS spikes, offering a means to test the proposed hypothesis.

Of note, individuals who experienced chickenpox years ago may shed infectious VZV in saliva [36] and thus theoretically may transmit VZV to others via coughing and sneezing. Additionally, subclinical reinfections of immunocompetent individuals with wild-type VZV have been reported [37,39-41], including a case of a 30-year-old man with herpes zoster caused by clade 5 VZV who experienced a second bout of zoster caused by clade 3 VZV four years later [40]. Such reinfections with wild-type VZV may be more common than previously thought [41], and may even occur in individuals previously vaccinated with the OKA varicella vaccine [40]. Thus, the asymptomatic transmission of clade 3 VZV by British troops to native Faroese during WWII is a possibility that warrants further investigation.

2.3. Evidence that Childhood VZV Clade 3 Infection Preceding Primary EBV Infection Causes MS

Given that the hypothesis posits that MS is caused by clade 3 VZV infection preceding primary EBV infection, the hypothesis can be further evaluated by examining how well it aligns with established epidemiological features of MS, as discussed below.

2.3.1. Alignment of the VZV Clade 3 Geographic Distribution with the 20th-Century Latitude Gradient of MS Prevalence in Europe and North America

In the 20th century, significant north-south high-to-low latitude gradients of MS prevalence were reported in North America and Europe that were frequently attributed to geographic distributions of populations with greater genetic susceptibility to MS and differences in ultraviolet light exposure [1]. Interestingly, these gradients also aligned with global climate features associated with latitude, with temperate climates found at higher latitudes and tropical climates found at lower latitudes that have been reported to influence VZV stability, transmission efficiency, and infection age [13-15]. Notably, approximately 90% of individuals living in temperate climates (where MS rates tend to be highest) contract primary VZV infections during childhood, whereas in tropical climates (where MS is rare), VZV initially infects adolescents and adults [13].

However, this pattern does not apply to Japan, a country with a predominantly temperate climate, high pre-vaccination era childhood varicella rates [27], and an extremely low MS prevalence rate (<5 cases per 100,000 persons) [1]. Nevertheless, this observation may support the proposed hypothesis, since over 98% of Japanese varicella cases are caused by clade 2 VZV infections [28], rather than infections by European VZV clades 1 and 3. which tend to occur in regions with much higher MS rates [25,26,34,42].

If VZV clade 3 is an MS trigger, its prevalence should align with 20th-century MS latitude gradients. This appears to be the case since VZV clade 3 prevalence has been reported to be highest in northern European countries with extremely high MS rates, such as Iceland, Finland,

and Germany [25,26] (https://www.atlasofms.org/map/iceland/epidemiology/number-of-people-with-ms). Nonetheless, to confirm this speculation, large VZV genotyping studies are needed to obtain "snapshots" of VZV genotypes circulating during 20th-century chickenpox epidemics across the U.S. and Europe, as reported in the abovementioned East London study [33].

If delayed EBV infection is an MS trigger, latitude-based differences in adolescent or adult EBV infection rates may align with the observed MS latitude gradient [7], as may distributions of different EBV strains at different latitudes [4, 43-46]. Together, the effects of clade 3 VZV and/or EBV on MS causation may be stronger at higher latitudes, as reflected by earlier ages of MS onset in such regions [47]. However, the strengths of MS latitude gradients may be changing, offering another opportunity to test the proposed hypothesis, as described in the next section below.

2.3.2. Changing VZV Clade Distributions May Explain Disappearing Latitude Gradients of MS Prevalence

In recent decades, the abovementioned MS prevalence gradients have been diminishing in certain regions and strengthening in others [47]. Since VZV is carried exclusively by humans, VZV clade distributions may reflect human population movements. Consequently, if VZV clade 3 contributes to MS risk, changes in MS gradients may be partially attributed to the movements of populations carrying VZV clade 3, including those in the U.S. throughout its history [48]. Such shifts in viral genotypes have been observed in East London, an area with a significant immigrant population, where gradual increases in the prevalence of clade 3 and clade 5 VZV are thought to have occurred between the 1920s and 1990s [33]. These changes in genotypic distributions have continued, as evidenced by the detection of more diverse VZV genotypes associated with recent varicella cases across Europe, as reported in 2009 and 2013 [25,34]. Meanwhile, migrations in the reverse direction have led to increasing proportions of clades 1 and 3 in Japan [28] and Mexico [49], where MS cases are rare but may be on the rise [1,17,29]. As a result, changing geographic distributions of VZV clade 3 in recent decades may be associated with diminishing MS latitude gradients in the U.S. and Europe and increasing MS incidence rates in Japan and Mexico, warranting further study. Furthermore, the introduction of VZV clades other than clade 3 into a population with significant clade 3 VZV circulation may lead to reduced clade 3 VZV infection rates due to inter-clade competition for hosts, potentially leading to lower MS incidence rates decades later when infected individuals reach the peak age range of MS onset (age 30). Therefore, if the hypothesis is correct, MS rates would be lower in regions with significant inter-clade competition compared to regions with high clade 3 circulation levels, and in regions with universal varicella vaccination programs (clade 2 VZV), potentially leading to diminishing MS latitude gradients.

In the early 21st century, the U.S., Japan, and several European nations introduced mandatory early childhood VZV vaccination, leading to significantly reduced numbers of varicella cases [50]. If clade 3 VZV is indeed involved in MS causation, the administration of the clade 2 OKA vaccine may attenuate the latitude gradient by decreasing MS rates in countries implementing vaccination, which tend to be located at latitudes where MS rates are highest. Such an effect could become apparent by the mid-2030s, when individuals who received the two-dose varicella vaccine as young children (beginning in 2006) reach their late 20s and early 30s, the peak age range of MS incidence [1]. Furthermore, if varicella vaccination prevents MS, pediatric MS rates should already be decreasing in vaccinated populations; however, no large-scale studies demonstrating such trends have yet been reported.

2.3.3. The Hypothesis May Explain the Increasing Female-to-Male MS Ratio Since WWII

In the 1940s, the female-to-male incidence ratio of MS in both northern and southern Europe was approximately 2:1. However, by the late 1980s, the ratio in northern Europe had risen to almost 4:1 in some regions, while remaining at 2:1 in southern Europe [51]. Although ascribing this trend change to sex-based differences in infection with clade 3 VZV versus other clades may be difficult, it could be consistent with sex-based differences in the timing of VZV and primary EBV infections. Interestingly, a study conducted in England and Wales during the pre-varicella vaccination era revealed sex-based differences in the ages of chickenpox and shingles cases. The study found greater chickenpox incidence rates in females than males aged 15–24, while equivalent shingles rates were observed between the sexes in this age group, and female shingles rates exceeded male rates in all other age groups [52]. Moreover, EBV seroprevalence rates and serum EBV-specific antibody levels were lower in adult males (ages 18-90 yrs.) than in adult females in Germany [53], suggesting either sex-based differences in delayed EBV exposure (which would not support the proposed hypothesis) or in immune responses to EBV that may contribute to higher female MS incidence rates, warranting further study.

The relationship between humans and herpesviruses has evolved during the 20th century due to various lifestyle-related factors. For instance, the replacement of breastfeeding with bottle feeding has led to reduced rates of infection with cytomegalovirus, a herpesvirus [54]. Additionally, improved hygiene has led to greater rates of delayed primary EBV infection and associated IM [55]. Meanwhile, increased enrollment of children in daycare facilities has contributed to higher rates of VZV infection at younger ages [56]. These combined changes may have disproportionately affected the MS susceptibility of females compared to males, potentially contributing to the increasing female-to-male MS ratio since WWII.

2.3.4. The Hypothesis May Explain Increasing MS Incidence in African Americans

A comprehensive study comparing MS incidence rates among African American and White U.S. soldiers in the Gulf War, Vietnam War, and WWII revealed intriguing findings. During WWII, the MS incidence rate for African Americans was lower than that of Whites. However, since that time, the African American rate has gradually increased and eventually surpassed that of Whites by 2013 [57]. This trend may support the proposed hypothesis, as lower EBV seroprevalence rates were observed in samples collected from preadolescent African American children (aged 9-11) in 2009-2010 compared to those collected in 2003-2004 [58].

Another possibility is that the increased mixing of different ethnic groups in recent decades may have facilitated the transmission of clade 3 VZV from Whites of northern European ancestry to African Americans, although VZV genotyping data from the U.S. are currently insufficient to confirm this claim. Alternatively, the historical underreporting of MS rates in non-White ethnic groups may have contributed to the observed increase in reported MS rates among African Americans, highlighting the need for further investigation [59].

2.3.5. The Hypothesis May Explain Different MS Rates Between Migrants and Non-Migrants

Investigations of MS risk in migrant populations have provided significant insights into potential causative factors of MS. Importantly, migration studies have revealed that future MS risk depends on MS prevalence rates in both origin and destination countries [4], as well as the age of migration [4,11,60,61]. Migrants moving from areas with low MS prevalence rates to regions with higher MS prevalence rates are protected from acquiring MS, while reverse migration offers varying degrees of protection depending on migration age and other factors [4]. Notably, second-

generation children born to migrants from low MS prevalence areas who relocate to high MS prevalence areas face a greater risk of developing MS than their first-generation immigrant parents, and in some cases may even have higher MS risk than natives in their adopted countries [11,61]. These findings indicate the existence of a protective factor exclusive to regions with low MS prevalence that can counteract the effect of later exposure to an MS-triggering agent.

In the context of the hypothesis proposed here, two scenarios involving migrants moving between areas of high and low MS prevalence can shed light on the effects of migration on childhood VZV clade 3 and EBV infection rates. In the first scenario, migrants moving at very young ages from regions of low MS prevalence (e.g., Japan, Africa) to areas of higher MS prevalence may be protected from getting MS, due to high early childhood EBV infection rates in their original places of residence [7]. This early exposure would increase their likelihood of contracting primary EBV before exposure to VZV clade 3 or other clades. Moreover, in their birth countries, they may have been exposed to non-European VZV clades 2 or 5, which could potentially protect them from MS if the disease is triggered by infection with VZV clade 3.

In the second scenario, migrants moving from areas with high MS prevalence to regions with low MS prevalence are less likely to be protected from developing MS compared to migrants in the first scenario. This is because they would likely contract clade 1 or 3 VZV infections during childhood while attending daycare or elementary school [62] unless they migrate at a very young age. However, depending on their ethnicities and/or socioeconomic status [7], a significant portion (approximately 20-50%) would not contract EBV until after age 15, since EBV infection tends to be delayed in populations with high MS prevalence rates. Consequently, many migrants moving from high to low MS prevalence areas may be exposed to VZV clade 3 during childhood (depending on their home country and year of infection [62]) before being exposed to EBV in adolescence or adulthood, thus retaining a greater MS risk regardless of their age at migration.

2.3.6. The Hypothesis May Explain Increasing MS Incidence Rates in Some Countries

Increasing incidence rates of MS have been reported in various countries over the latter half of the 20th century, although some of these reported increases may be attributed to factors such as better case ascertainment and improved access to medical care [1]. However, a comprehensive retrospective study conducted in Denmark, a country with high MS incidence rates, excellent medical care, accurate MS case identification, and no universal varicella vaccination program, revealed a doubling of MS rates in women between 1950 and 2010 (with only modest increases observed in men) [63]. This upward trend in MS incidence may be explained if rates of VZV clade 3 infection and/or delayed EBV infection have disproportionately increased in Danish women since WWII.

Notably, a 2019 Danish study reported that EBV seroprevalence in 10-year-olds was relatively low (~41%) [64], suggesting that rates of delayed EBV infection may have risen in Denmark. However, no available data on earlier EBV seroprevalence rates or VZV genotypes in Denmark could be found, although it is likely that the VZV seroprevalence rate in 10-year-olds is high in Denmark, as in other northern European countries [62]. Thus, it is plausible that increasing MS rates in Denmark are linked to a rise in clade 3 VZV infection and delayed EBV infection, warranting further study.

2.3.7. The Hypothesis May Explain the Extremely High MS Rate in Sardinia, Italy

MS prevalence in Sardinia, Italy, an island in southern Europe, is among the highest worldwide (330 cases/100,000 population) [65], breaking the 20th-century latitude gradient rule. If the hypothesis is correct, the extremely high Sardinian MS rate may be explained by a high early

childhood clade 3 VZV infection rate coupled with a high delayed EBV infection rate. 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 Sardinian adults [66], compared to rates elsewhere in Italy and globally [67,68]. 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 [69]. These findings suggest that uniquely high MS rates in Sardinia may result from the combined effects of both hypothesized risk factors, warranting further investigation.

2.4. Testing the Hypothesis

The simplest approach for testing the hypothesis would involve VZV genotyping to identify VZV clades present in zoster skin lesion specimens [70], saliva [71], or throat swabs [72] obtained from MS patients with shingles, similar to the approach used for the single MS patient described in [32]. If only clade 3 VZV is detected in specimens from MS patients, this would support the proposed hypothesis.

However, since 2006, many MS patients have received shingles vaccinations (containing the clade 2 VZV OKA strain) before starting immunomodulatory MS treatments and thus are protected from shingles. In the absence of zoster skin lesions, obtaining specimens for VZV genotyping is challenging, as latent VZV is present in cells and body fluids at extremely low levels. Nonetheless, it may be possible to successfully amplify DNA for VZV genotyping from other sources in MS patients without zoster, such as white blood cells from older MS patients [73] or relapsing MS patients [18,19], saliva from MS patients receiving fingolimod treatment [74], or saliva from patients under stress [36]. Importantly, individuals who have been vaccinated with the OKA vaccine harbor both vaccine VZV (clade 2) DNA and wild-type VZV DNA acquired from varicella infections that occurred before varicella vaccination.

If the first MS trigger is confirmed to be clade 3 VZV, the hypothesized sequence of events in MS causation, specifically VZV preceding primary EBV, could be confirmed through large-scale frequent monitoring of varicella and EBV seroprevalence rates in countries with low varicella rates, no varicella vaccination programs, and rising MS rates to correlate seroprevalence profiles with MS onset.

Alternatively, monitoring of MS rates in Sicily, where a single-dose varicella vaccine was administered to 70% of 15-month-old children born in 2005 [75], and in other countries with longstanding varicella vaccination programs [76] could be conducted, with decreasing MS rates by 2035 supporting the hypothesis.

3. CONCLUSIONS

This paper presents a hypothesis suggesting that MS in genetically predisposed individuals is caused by two herpesvirus infections: childhood VZV clade 3 infection (based on a single VZV isolate from an MS patient) and delayed EBV infection. If the hypothesis is correct, varicella vaccination may prevent MS, while drugs that inhibit the reactivation of latent VZV and EBV infections may slow disease progression in existing MS patients.

The most direct way to test the hypothesis would be to determine whether the genotypes of VZV isolates from MS patients are exclusively clade 3 VZV. Should the results confirm an association between VZV clade 3 and MS, the investigation should next extend to determining whether the sequence of VZV and EBV infections influences MS risk.

In the meantime, monitoring adult and pediatric MS rates in countries that have implemented VZV vaccination programs [76] may reveal that the OKA vaccine (clade 2) has a protective effect against MS. If evidence supports this effect, countries without varicella vaccination might consider adopting such programs for MS prevention, especially those with high MS incidence rates.

Furthermore, if primary EBV infection following VZV infection triggers MS, this knowledge should inform the development of EBV vaccination protocols currently under consideration. Humans have coexisted with herpesviruses for much of their history, but lifestyle changes and increased migration may be altering our relationship with these viruses, with unintended consequences. The order of VZV, EBV, and other herpesvirus infections (CMV, HHV-6, HHV-7, HHV-8, and herpes simplex 1 and 2), may play a crucial role in maintaining human health. Understanding these dynamics could help prevent dysregulation of viral gene expression in infected hosts, potentially reducing the risk of developing MS.

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