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Hypothesis

Chickenpox as An Evolutionary Trigger for Migraine: A Hypothesis

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Abstract

On the surface there does not appear to be a connection between chickenpox and migraine but, on closer examination, both conditions are associated with neuroinflammation and, because almost every human throughout history was infected with the varicella-zoster virus, it is possible that it could have triggered certain medical disorders in our ancestors. We propose a hypothesis that the acute chickenpox infection may have contributed to the appropriate environment to prime the brains of early humans for migraine. Several inflammatory mediators and immune cells involved in migraine also participate in the immune response to primary varicella infection. This, together with the fact that the virus establishes chronic latency in the trigeminal ganglia, may have contributed to a sensitized trigeminovascular system that could produce migraine if the correct susceptibility genes and exposures were present. These postinfectious neuroinflammatory reactions would also have the capability of producing a hyperexcitable cortex, hypothalamic generator and cortical spreading depression, which are the key components of migraine pathophysiology. Other supporting observations include the coexistence of varicella-zoster virus and migraine in early humans, the fact that chickenpox occurs prior to the age of migraine onset in most individuals, and the recent recognition that the proportion of US migraine patients with moderate-to-severe disability rose from 22.0% to 42.4% following implementation of the varicella vaccination program. We propose that chickenpox may have acted as an evolutionary trigger for migraine.

Introduction

Two of the most common and ancient medical conditions are chickenpox and migraine. Both were present in our early human ancestors.[1,2] Chickenpox historically occurred in almost every person worldwide before the recent immunization programs, and migraine is a worldwide syndrome affecting over 1 billion individuals.[3,4] Migraine may have an evolutionary advantage for affected individuals, but why did humans ever produce this disabling condition in the first place?[2,5] Did it arise *de novo* or did something need to prime the nervous system for its initiation? On the surface there does not appear to be a connection between chickenpox and migraine but, on closer examination, both conditions are associated with neuroinflammation with specific cytokine, chemokine and immune cell production and the trigeminal system, which has a central role in migraine, is also the system that varicella-zoster virus (VZV) infects and establishes lifelong latency.[6,7] We thus propose a hypothesis that being infected with chickenpox may have been an evolutionary trigger of migraine. We evaluate the hypothesis by looking at various parameters including evolutionary coexistence and spread, timing of VZV infection and migraine onset, shared immune mechanisms with a kindling model, and the linkage between VZV infection and specific migraine pathophysiologic substrates including cortical spreading depression (CSD), cortical excitation and hypothalamic modulation. In addition, potential considerations include possible public-health and clinical consequences of the hypothesis based on recent alterations in migraine epidemiology after the start of varicella immunization programs. Finally, future directions for testing the hypothesis will be discussed.

Chickenpox is caused by the VZV, which belongs to the α-herpesvirus family. Also called human herpesvirus 3, VZV has a double-stranded DNA genome.[8] Herpesviruses have specific hosts

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and VZV is thus a human-only virus. Primary VZV infection causes chickenpox, whereas viral reactivation causes herpes zoster or shingles. VZV is unique among herpesviruses as it is the only one that primarily transmits via aerosolized droplets, making it quite effective for horizontal transmission and epidemic spread.[8,9] VZV also establishes latency in sensory ganglia including cranial, dorsal root, and autonomic ganglia.[10] Latency can last decades prior to full reactivation. Finally, it is a single serotype; thus, one chickenpox infection leads to lifetime immunity.[11] Before the introduction of the varicella vaccine, chickenpox was considered a normal pediatric illness.[11] It was endemic and around 90% of children developed the acute infection by the age of 10 years. For example, the peak prevalence of chickenpox in the United States was from ages 4 to 10 years while peak age-specific incidence was between 1 and 6 years of age.[11,12] Chickenpox has different age distributions depending on location. In temperate regions it is apparently more contagious and mainly affects young children while in tropical climates it is less transmissible and leads to an older age of onset primarily affecting adolescents and adults. Seasonal predilection is typically winter and early spring in temperate regions while it varies more by location in tropical countries.[11]

Migraine is a chronic neurologic syndrome marked by acute attacks with phases that include the prodrome, aura, headache and postdrome.[13] Not all individuals have each phase, and each phase may have a distinct pathogenesis. The headache itself includes moderate to severe trigeminal-based head pain that may be unilateral or bilateral, may switch sides, may be pulsatile, and may be associated with nausea and/or vomiting and phonophobia and photophobia.[14] Migraine as a syndrome can be episodic or chronic depending on the number of headache and migraine days per month. Migraine incidence peaks in mid-teens to early twenties while prevalence has a bimodal peak of late teens to twenties and around age 50 years.[15,16] Migraine is a trigeminal-based neuroinflammatory condition in which the headache phase involves activation of trigeminal sensory afferents whose cell bodies originate in the trigeminal ganglia and that innervate the meninges and their blood vessels. These afferents send signals centrally to second-order neurons in the trigeminocervical complex and then to third-order neurons in the thalamus and finally to the cortex.[13] The pain of migraine involves the concomitant release of specific neurotransmitters and cytokines which result in neurogenic inflammation and neuroinflammation.[17] A central generator is likely located in the hypothalamus. Finally, there is a "migrainous brain" marked by a hyperexcitable cortex that causes a persistent susceptibility to environmental triggers.[18]

Hypothesis

The acute chickenpox infection may have created an appropriate neuroinflammatory/neuroimmune environment to kindle the brain of early humans to produce migraine. Several inflammatory mediators and immune cells implicated in migraine, both ictally and interictally, overlap with those involved in the immune response to primary VZV infection. This observation, together with the fact that the virus establishes chronic latency in trigeminal and dorsal root ganglia and that the latent infection is probably more active than previously thought with intermittent or constant immune activity, may have contributed to a sensitized trigeminal system that would produce migraine if the correct susceptibility genes and triggers/exposures were present.[19] These postinfectious neuroinflammatory reactions would also have the capability of producing a hyperexcitable cortex, hypothalamic generator and CSD which are the key components of migraine pathophysiology. There have been suggestions that viruses may play a role in migraine pathogenesis but not from an evolutionary standpoint and there has been no proposal that chickenpox was the possible evolutionary trigger. The ultimate question based on the proposed hypothesis and in the face of the recent varicella vaccine programs and in essence the near eradication of chickenpox in some countries, is there now a set migraine system which has been passed down over eons and no longer requires a VZV infection to activate it or do modern humans still require the viral kindling event and migraine evolution will now be forever altered because of immunization?

Evaluation of the hypothesis

The proposed hypothesis that viral infections during early human ancestry influence current human biology has precedent. Approximately 8% of the modern human genome consists of endogenous retroviral sequences derived from ancient exogenous viral infections. These early infections may have helped establish human biological mechanisms, including host immunity and nervous system development.[20] Recent studies have also linked the activation of human endogenous retroviruses to neuroinflammatory and neurodegenerative conditions.[21]

Evolution

Early human neuroanatomy and migraine susceptibility genes

The trigeminal nerve and the trigeminovascular system have been present in jawed and some jawless vertebrates for hundreds of millions of years and were present in our early human ancestors.[22,23] Migraine genetics is a relatively new field with the first monogenic syndrome discovered in 1996 and the first susceptibility gene locus in 2010. There are now over 180 susceptibility gene loci for migraine.[24,25] These genes were also likely present in early humans because they may have conferred a possible evolutionary advantage on individuals with migraine compared with individuals without migraine.[2] The fact that migraine susceptibility genes have been found in postmortem trigeminal ganglia supports the possibility that these genes were present in early human neuroanatomy.[26] In addition, migraine risk-associated genes that allowed individuals with migraine to migrate and survive in more northern, colder latitudes date back at least to around 8,000 years ago.[27]

VZV during early human evolution

Herpesviruses date back millions of years to the time of the dinosaurs and were present at the onset of human ancestry.[1] VZV in some form may have existed early in human evolution, although the timing of its divergence from related viruses and the most recent common ancestor of currently circulating VZV strains remain uncertain.[28,29] It is also uncertain whether the current strains of VZV originated in Africa at the time of human worldwide distribution or originated in Europe as a much more recent event.[8] Thus, the current form of VZV may be different from the original virus that infected early humans. The lack of ancient VZV

DNA limits evolutionary assessment. It is likely, however, that almost all early humans were infected by VZV; its relatively stable double-stranded DNA genome, efficient transmission, and capacity for latency may have conferred a survival advantage and contributed to a near-100% infection rate over millennia until the recent immunization programs originating in the mid-1990s.[1]

Early coexistence of migraine and VZV

Headache and migraine most likely have been present since the time of *Homo sapiens* (modern humans) around 300,000 years ago and probably date back millions of years with earlier human lineages.[2,5] The first writings depicting migraine come from 2000 BCE.[30,31] As migraine is a highly disabling condition it has been suggested although never proven that having migraine in early humans could establish an evolutionary advantage. It has been hypothesized that the hyperexcitable cortex and sensitized trigeminal system of an individual with migraine would allow affected individuals to be alerted to danger sooner than individuals without migraine and thus gain a higher chance of survival.[2,5] The fact that migraine has persisted for so long would also explain why the phenotypic presentation has not really changed since its original description and that the only substantial changes in migraine have arisen from evolving secondary exposures especially since the industrial revolution (environmental toxins, tobacco, alteration of diet with increased obesity, climate change).[30]

Timing of chickenpox infection and migraine onset

For VZV to have a triggering role in migraine pathogenesis it would have to occur before migraine onset in affected individuals. In most instances around 90% of children will develop chickenpox prior to the age of 10 years with many having the infection between 1 and 6 years of age.[11,12] It is possible that the earliest strains of VZV could have caused an infection at an even younger age. Migraine is also a disorder of young people but typically starts in adolescence. The peak age of migraine incidence worldwide reported in the Global Burden of Disease Study (GBD) 2021 was 10–14 years thus older than chickenpox onset.[32] In temperate countries like the United States where the onset of varicella infection is overall younger, migraine incidence peaks between the ages of 15–19 years in males and 20–24 years in women.[15] In tropical countries like Singapore where the age of developing chickenpox is typically older, the average age of varicella infection ranges from 5–24 years with around 60% of children under 15 being seropositive for the infection.[33] The mean age of onset of migraine in Singapore is 26 years consistent with chickenpox onset preceding migraine onset.[34] As chickenpox is ubiquitous and affects almost everyone and does not have a gender preference, the prevalence of migraine should be the same in boys and girls if chickenpox is indeed the kindling event. This would change at adolescence when estrogen becomes a prominent trigger for migraine in women and alters the gender ratio. Indeed, migraine epidemiology notes equal gender prevalence until the time of puberty, thus helping the proposed hypothesis.[16]

Proposed global co-diffusion of VZV and migraine

If VZV was required to trigger migraine then as humans migrated out of Africa, migraine would also have migrated along with VZV if it was not to become an extinct syndrome. Phylogeographic studies have identified VZV clades with distinct geographic distributions and estimates of the timing of their common ancestry vary.[29] Phylogeographic analysis examining the origin of extant VZV clades has suggested Europe as the probable point of origin rather than Africa.[8] There is genetic data also placing migraine in Europe around the same time as the proposed modern strain of VZV.[27,29] A unique allele (rs10166942) linked to the *TRPM8* gene, which encodes for a cold receptor localized to the dorsal root ganglia and has also been shown to be a genetic risk factor for migraine, was found to originate in Africa, but through positive selection reached its highest frequency in Europe.[27] Of note, individuals of European descent have the highest prevalence of migraine in the modern age.[27]

VZV characteristics relevant to migraine pathogenesis

Involvement of the trigeminal and dorsal root ganglia

During acute infection VZV sets up latency in cranial, dorsal root and autonomic sensory ganglia along the neuroaxis preferentially affecting the trigeminal ganglia.[10] The trigeminal ganglia and trigeminocervical complex are the main neuroanatomic hubs of migraine-based pain, but the upper cervical dorsal root ganglia are also believed to be involved in the occipital pain of migraine as they innervate the dura over the posterior fossa and initiate in calcitonin gene-related peptide (CGRP)-containing neurons.[35]

VZV latency

Once the primary immune/inflammatory peak occurs with varicella infection that hypothetically kindles the migraine system, how does this turn into a chronic headache syndrome? Latency of VZV in sensory ganglia may be the key. It is now suggested although not completely established that the "latent" virus is not completely dormant, but there are periods of immune activation to the virus to keep it in its latent state.[19,36-38] The probable result of these episodes of immune activation with cytokine/chemokine production would be an enduring sensitization of the trigeminal system lowering its threshold for activation and thus a persistent susceptibility leading to a chronic headache disorder.

Kindling model

The acute event

Chickenpox needs to cause a substantial neuroinflammatory/neuroimmune response that primes the trigeminovascular system so from that initial infection migraine will occur at some point in that susceptible individual's lifetime. Headache is one of the most common prodromal symptoms of chickenpox.[11] This suggests a positive priming event in that the neuroinflammatory cascade caused by VZV infection can indeed activate the trigeminovascular system to cause head pain. Interestingly, headache is not mentioned as a side effect of the varicella vaccine which is a live but attenuated virus which also causes a neuroinflammatory response similar to, but less intense than, that caused by the wild-type virus.[38] Thus, the intensity of response to acute wild-type VZV may be required to kindle migraine or at least the migraine that has been documented from its earliest descriptions. A possible kindling model (also based on neuroinflammation and herpesvirus infections) which is similar to what is proposed for migraine has been suggested for virus-triggered epilepsy.[39] The individual gets their first ever seizure with the initial viral infection, and recurrent seizures come later in life to produce a chronic neurologic syn-

drome. The same proinflammatory cytokines proposed in our model (see below) are suggested as inciters in the epilepsy model.[40] Available evidence suggests in both migraine and epilepsy, the viral insult leads to the main symptom of the disease (seizure or headache) but the brain alterations typically take time to eventually lead to the syndrome.

For the proposed kindling model to be valid, the neuroinflammatory and neuroimmune responses induced by VZV infection would need to overlap with those involved in migraine pathogenesis.

Immune responses during acute VZV infection

The complete immune response to VZV is complicated and beyond the scope of this manuscript. In brief, during acute infection the virus replicates in respiratory epithelial cells and then is transferred to T cells in the tonsillar lymphoid tissue. The VZV-infected T cells then deliver virus to the skin (rash of chickenpox) and to the sensory ganglia where it establishes latency.[41] VZV infection leads to neuroinflammation with both chemokine and cytokine production. Natural killer (NK) cells and T cells produce interferons including IFN-α, IFN-β, and IFN-γ which are necessary to prevent viral replication. Pro-inflammatory cytokines IL-1β, IL-6, IL-8 and TNF-α are also produced as well as the chemokines CCL-2, CCL5 and CXCL10.[7,41,42] This helps attract immune cells (macrophages, monocytes, T cells, NK cells) to the site of the infection to control viral spread and elicit an inflammatory response. Regulatory cytokines are also made to quell the proinflammatory cascade including TGF-β (response to sensory ganglia infection) and IL-10.[42] Proinflammatory cytokines can have positive effects for the host by containing the infection but if there is excessive production this can lead to neuronal and tissue damage. IL-1β, IL-6, and IL-8 can all cause nerve injury and sensitization.[41] If VZV leads to central nervous system (CNS) infections including encephalitis, meningitis and vasculitis there is even a more robust chemokine response including elevated levels in the cerebrospinal fluid of CXCL8 (attracts neutrophils), CXCL9, CXCL10 and CCL19 (attracts T cells) as well as an elevation of matrix metalloproteinase 2 (MMP-2) which interrupts the blood–brain barrier. If viral encephalitis occurs then cerebrospinal fluid levels of MMP-3, MMP-8, and MMP-12 are also elevated.[43] One can hypothesize that the initial strains of VZV infecting early humans were more virulent than current strains; in addition, early human ancestors lived in an environment without good hygiene, antiviral or antipyretic medications. The risk of VZV-induced CNS infections was therefore probably higher, which would have led to a more robust neuroinflammatory response helping to further sensitize the trigeminovascular system and cortex. Even today with established modern medical care, VZV is still considered one of the most common viruses that lead to CNS infections.[42]

Immune surveillance during VZV latency

The full immunologic basis of VZV latency is not completely understood. Is it a state of quiescence until full reactivation or a period of continuous or intermittent host immune surveillance? Recent studies favor the latter.[19,36-38] It has been suggested that there is at least intermittent viral gene expression during latency leading to an antigenic response involving T cells, NK cells, macrophages and B cells leading to persistent immune monitoring by the host.[7] The antigenic activity is without viral replication and/or active infection and thus not associated with zoster.[38]

Neuroinflammation in migraine

The pathogenesis of migraine is complicated. It has become increasingly recognized that both neurogenic inflammation (sterile inflammation at the meninges) and neuroinflammation (activation of immune cells to produce modulators of inflammation) play substantial roles in migraine initiation, trigeminal sensitization and possibly chronification.[13] The profile of cytokines, chemokines, neurotransmitters, and immune cells active in migraine is remarkably similar to the inflammatory profile noted with acute and latent VZV infection. The role of immune cells and proinflammatory cytokines in migraine is to directly activate and sensitize meningeal trigeminal afferent neurons and recruit immune cells to the meninges and trigeminal ganglion to further promote nerve sensitization.[6] They can also alter neurotransmitter release leading to cortical and neuronal excitation.[17] The following are shared inflammatory mediators between VZV and migraine although VZV-migraine-specific patterns have yet to be characterized.

Shared inflammatory mediators and mechanisms

Cytokines, chemokines, and neuropeptides

Proinflammatory cytokines IL-1β, IL-6, IL-8 and TNF-α which are all elevated during acute VZV infection are increased in the serum of migraine patients versus controls (TNF-α and IL-6 more interictally and IL-1β ictally).[6,17,44] TNF-α, IL-1β and IL-6 sensitize trigeminal sensory afferents. The main neuropeptides released during a migraine headache and involved in neurogenic inflammation are CGRP, substance P and pituitary adenylate cyclase-activating peptide (PACAP).[13] IL-1β can stimulate CGRP release from neurons in the trigeminal ganglia.[45] CGRP then causes neurogenic inflammation via trigeminal sensory afferents on the meninges and CGRP itself also leads to the release of proinflammatory cytokines from T cells. Studies have shown that CGRP levels are heavily dependent on both IL-1β and IL-6 levels.[45] The human varicella latency protein IE63 is involved in trigeminal nerve persistent infection and causes an increase in CGRP release from trigeminal neurons.[46] Thus, chickenpox may have provided a potential evolutionary context for CGRP involvement in migraine pathophysiology. Models have also suggested increased substance P levels during acute varicella infections in response to nerve and skin irritation.[47] PACAP has not yet been studied in VZV infection. IL-10 which inhibits inflammation, is also elevated during both acute varicella infection and migraine attacks.[6,42] Chemokines CCL2 and CCL5 which are active during chickenpox are also increased interictally in individuals with migraine.[6,42] CCL2 is produced in trigeminal ganglia neurons and activates T cells and macrophages. These immune cells have been shown to enhance CGRP and PACAP signals in the trigeminal ganglia thus leading to heightened nerve sensitization.[48]

Cortical spreading depression

The neurophysiologic event that causes migraine aura has a bidirectional relationship with cytokines and chemokines. CSD can cause the release of IL-1β, IL-6, TNF-α and CCL2 which can activate microglia to produce further cytokine release which then lowers the threshold for subsequent CSD initiation.[42] In addition, IFN-γ can lower the threshold for CSD initiation.[49] It is possible that the cytokine/chemokine activation created by VZV infection

early on in human history influenced CSD pathogenesis and the production of the migraine with aura phenotype.

Cortical excitation

Proinflammatory cytokines released during VZV infection and then subsequently migraine attacks can play a role in the pathogenesis of the hyperexcitable cortex of migraine which is felt to be primarily driven by glutamate. Both TNF-α and IL-1β have been shown to alter N-methyl-D-aspartate and AMPA glutamate receptors by increasing their Ca^{2+} permeability. In addition, they also cause endocytosis of GABA channels and inhibition of GABA-mediated calcium influx.[39] IL-6 has been noted to alter glutamate receptor function and glutamate clearance.[50] This creates an imbalance between neuronal excitation and inhibition which could produce the hyperexcitable cortex observed in migraine.

Immune cells

During the interictal period of migraine there is a significant elevation in CD4+ T cells and a decrease in CD8+ cells.[6] This pattern indicates persistent immune dysregulation. This same pattern is possibly noted in VZV-infected patients.[51] CD4+ T cells appear to be needed for immune surveillance and latency of VZV in addition to being activated during the initial viral insult, while CD8+ cells are elevated and active during acute VZV infection but appear to have a more limited role chronically and with low prevalence in latently infected trigeminal ganglia.[7,51] Therefore, the immune status of latency is comparable to the immune state of migraine between attacks.[17]

Table 1 summarizes the immune/inflammatory agents that are involved in both chickenpox and migraine.[6,7,17,41-44]

Other non-inflammatory linkages between VZV infection and migraine pathogenesis

Hypothalamic generator

The hypothalamus is the potential generator of migraine attacks based on various observations. The reason why the hypothalamus becomes active prior to headache initiation is unknown. Could it be in part because of varicella infection and its potential modulation of hypothalamic activity? In the modern age it is rare to see hypothalamic involvement during acute chickenpox infection, but it can occur.[52] There are also reported cases of post-chickenpox narcolepsy suggesting both hypothalamic changes after VZV infection and alterations in orexin levels which have a potential role in migraine pathogenesis as they modulate trigeminal activation.[53,54] In addition, the proinflammatory cytokines released during chickenpox alter blood–brain barrier permeability thus increasing the risk for CNS and possibly hypothalamic invasion.[41] Finally, a possible interaction between hypothalamic biology and VZV-related processes as chickenpox infection rates have a circadian periodicity and age of onset/infectivity is altered by the distance to the equator.[11]

Cortical spreading depression and aura

There are no documented cases of chickenpox causing migraine with aura noted in the literature; however, there are isolated reports of acute VZV infection in children (with family history of migraine without aura and thus presumed susceptibility genes) leading to metamorphopsia or Alice in Wonderland syndrome, which may represent a form of migrainous aura.[55] This suggests a potential connection between chickenpox infection and CSD initiation.

Migrainous cortical excitation

In regard to cortical hyperexcitability and its clinical manifestations including photophobia and phonophobia, there are defined case series describing these symptoms along with headache during acute chickenpox infection with associated meningoencephalitis.[56,57] This indicates a possible activation of cortical excitation which is a setup for a "migrainous brain" in patients who develop CNS complications with acute VZV infection.

Persistent changes in the trigeminal nerve

Concerning trigeminal nerve changes after VZV infection that could potentially be seen in migraine and part of its underlying pathogenesis, there is recent magnetic resonance imaging (MRI) data showing reduced fractional anisotropy in the trigeminal nerve root entry zone in patients with episodic migraine.[58] These changes were not seen in non-headache controls. These findings suggest microstructural abnormalities that may reflect distortion in myelin organization or true demyelination. Similar findings of reduced fractional anisotropy have also been noted in patients with acute herpes zoster infection, postherpetic neuralgia and primary trigeminal neuralgia, which can be virus-induced.[59,60] MRI studies in acute chickenpox and early trigeminal latency have not been performed. There is thus a possible pathologic alteration of the trigeminal nerve, potentially associated with VZV infection that could link to the trigeminal nerve changes noted on MRI in individuals with migraine, further supporting the proposed hypothesis. This needs further investigation.

Migraine susceptibility genes in human trigeminal ganglia without a history of headache

Evaluation of human trigeminal ganglia by LaPaglia *et al*.[26] found numerous migraine susceptibility genes in 16 postmortem samples from individuals without a documented headache or migraine history (age range 18–64 years). One would assume that not all or even any of the individuals had migraine, strengthening our hypothesis that the migraine anatomy is present in humans, but something needs to prime the system, like a VZV infection, to initiate the process.[26]

Viral infection and headaches with migrainous features

New daily persistent headache (NDPH) is a type of primary headache that begins abruptly and occurs daily and can continue for months to years without remission. A substantial proportion of NDPH patients can have migrainous features to the extent that phenotypically it cannot be distinguished from chronic migraine without knowledge of the temporal profile of onset.[61] The leading recognized trigger for NDPH is a viral infection (>20% of patients) with linkage to herpetic viruses (cytomegalovirus, Epstein-Barr virus) and non-herpetic parvovirus and COVID-19.[62,63] This strengthens the concept that a single viral infection can cause a migraine-like headache disorder.

Other potential viruses

In addition to VZV, herpes simplex virus type 1 (HSV-1) is another alphaherpesvirus that can establish latency in sensory ganglia and has a relatively high infection rate in young children.

Table 1. Comparison of cytokines and chemokines investigated in VZV infection and migraine

Immune issue	VZV infection	Migraine
Cytokines		
IL-1β*^	↑	↑
IL-6*^	↑	↑
IL-8*^	↑	↑
IL-10*^	↑	↑
IL-12	↑	↑
TNF-α*^	↑	↑
TGF-β	↑	↑
IFN-γ	↑	↑
Chemokines		
CCL2	↑	↑
CCL5	↑	↑
Matrix metalloproteinase		
MMP-2	↑	↑

*Most Extensively Studied in Varicella Zoster Virus Infection.[7,41,42] ^Most Extensively Studied in Migraine.[6,17,42,44] ↑ increased levels.[6,7,17,41-44] CCL2, C-C motif chemokine ligand 2; CCL5, C-C motif chemokine ligand 5; IFN-γ, interferon gamma; IL, interleukin; MMP-2, matrix metalloproteinase-2; TGF-β, transforming growth factor beta; TNF-α, tumor necrosis factor alpha; VZV, varicella-zoster virus.

A recent study did find a positive correlation between HSV-1 seropositivity and migraine showing a twofold increased risk in HSV-1-positive patients.[64] Thus, it is feasible that HSV-1 and not VZV was the evolutionary inciter of migraine. However, several points favor VZV. First, the overall seroprevalence for HSV-1 in children is less than VZV but does vary by country. In the United States only 28% of children under 10 years of age and 36% between 10–19 years were seropositive, while 32% of children in Europe (under age 20) tested positive.[65,66] In Africa 44% were seropositive among children aged 5 years or younger and up to 85% between 6 and 15 years of age.[67] This compares to VZV with a seroprevalence of >90% during childhood.[11] Second, the initial infection is much more dramatic with VZV and thus one would assume a much higher neuroinflammatory response acting as a primer for trigeminal system activation compared to HSV-1 which typically may be milder or even asymptomatic in clinical presentation.[68] Third, the largest postmortem studies show a higher frequency of VZV in the trigeminal ganglion than HSV-1.[69] Fourth, the latent infection leading to cranial neuralgia syndromes is a hallmark of VZV but not HSV-1. Finally, one cannot rule out the need for coinfection of these two viruses for migraine occurrence in early humans and/or VZV being the true trigger but HSV-1 acting as an exacerbator such as in status migrainosus or migraine chronification in modern humans.

It is also feasible that any herpetic virus including cytomegalovirus, Epstein-Barr virus, human herpesvirus 6, HSV-1 or HSV-2 and VZV could trigger migraine in modern humans as the trigeminal system has already been evolutionarily altered by VZV to develop migraine and passed down over time so the priming virus no longer has to be varicella alone.[70-72]

Figure 1 is a graphical representation of the proposed hypothesis and potential consequences.

Consequences of the hypothesis

Public health consequences: potential changes in migraine epidemiology

The alteration is proposed to have been made by the varicella virus to the early human trigeminovascular system to kindle migraine and to have been passed down for hundreds of thousands to millions of years. In addition, as chickenpox is ubiquitous its presence may still be necessary even today to trigger the migraine process. Hence, the recent change to the natural history between chickenpox and humans based on the varicella immunization programs (1990s–present) which in some countries have nearly eliminated acute varicella infections could lead to modifications in migraine epidemiology/evolution.[73] Interestingly, some distinct changes in the epidemiology of migraine have occurred since the 1990s that parallel the institution of the first vaccine program.

The vaccine

The varicella vaccine is a live attenuated vaccine (Oka strain). It was first developed in Japan in 1974.[38] It currently comes as monovalent and quadrivalent (measles, mumps, rubella and varicella-MMRV) forms. Dosing strategies can be a single dose which can reduce severity of illness but is prone to breakthrough infections while a two-dose strategy can virtually eliminate the disease (>95% effective in prevention).[38] The United States in 1995 was the first country to adopt a universal vaccination program. This was initially a single dose while they were also the first to add a second required dose in 2006.[73] This strategy led to a dramatic decline in chickenpox cases from more than 4 million to less than 150,000 (97% decrease).[74] More importantly, a substantial reduction in hospitalizations and deaths occurred. At present, around 45 countries have instituted a universal vaccine

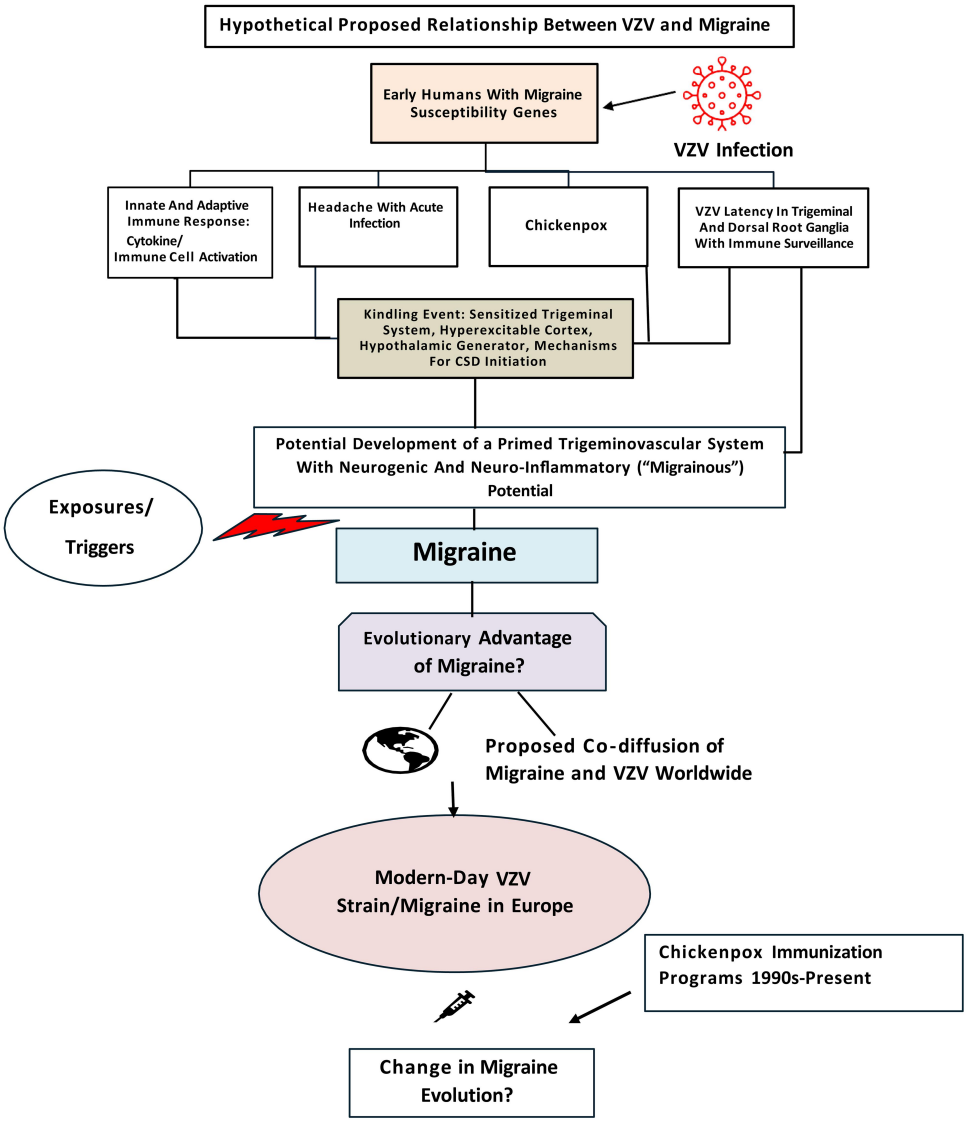


Fig. 1. Proposed hypothetical relationship between chickenpox/VZV and migraine evolution. BCE, before common era; CSD, cortical spreading depression; VZV, varicella-zoster virus.

program for infants while only 28 countries have a two-dose regimen.[73] Part of the reason for not offering the vaccine is not economic in all cases but a concern for increased herpes zoster infections in an aging population. Therefore, in some nations chickenpox has become uncommon whereas in others it remains a typical childhood illness.

The dosing strategy in the United States for children is first dose at 12–15 months and second dose at 4 to 6 years of age.[38]

Epidemiologic alterations

The United States was the pioneer in implementing a mandated varicella vaccine program for all children who were to be enrolled in public schools or daycares. It has one of the highest if not the highest chickenpox elimination rates worldwide.[74] Based on these features, if any country would have noted a change in migraine epidemiology since the alteration of chickenpox incidence it would be the USA. A recent study looking at 11 population-based studies in the United States over a 30-year time period starting 6 years prior to the varicella immunization program to 12 years after the second dose was mandated noted that while migraine prevalence remained stable, migraine-related disability has increased substantially.[75] The percentage of the migraine population with moderate to severe disability based on Migraine Disability Assessment scores has increased from 22.0% in 2005 to 39.0% in 2012, to 42.4% in 2018.[75] In addition, the frequency of headaches has increased over time with more individuals developing either high-frequency migraine or chronic migraine (6.8% in 2005 to 11.7% in 2018). Suggestions on why this has

occurred, including environmental triggers, have been discussed but there are still many unknowns.[75] Because these trends occurred after the second dose of the varicella vaccine was initiated, it is worth investigating whether the vaccination program is associated with these epidemiologic changes. However, this temporal association does not establish causation.

If any group would show the earliest changes in migraine epidemiology with the reduction in chickenpox, it is young children and early adolescents as that is the primary target group of VZV infection and immunization. Only 4 of the studies reviewed by Cohen *et al*.[75] included pediatric populations (ages 12 and older) so the full picture of what is happening to children is not completely known although the child population did show higher migraine disability scores over time. The study results, however, may have underestimated changes that might have been observed if children under 10 were included (which is the immunized population).

From GBD studies over the past 3 decades (1990 to 2019) there has been a 40% increase in the annual number of incident migraine cases worldwide. The group with the highest incidence rate was ages 10–14 years.[76,77] The United States was one of the leading countries with the largest change in incidence since before the varicella vaccine to a decade plus postvaccination program. Population growth and demographic changes should also be considered when interpreting these temporal trends.[75,77] Other explanations, including lifestyle changes, stressors, environmental triggers, and better diagnostic strategies are all feasible but there has been no reference to immunization for chickenpox as an additional factor.

Other early adopters of universal varicella vaccination included Puerto Rico, a U.S. territory, and Uruguay, and both have two-dose regimens. Puerto Rico started its program in 1996 and added a second dose in 2007, while Uruguay initiated in 1999 with a later second dose in 2014.[73] These are small jurisdictions and there is very limited data on migraine epidemiology especially trends over time. In the recent Americas' Migraine Observatory Study, Uruguay did have the 4th highest prevalence of migraine in the Pan-Americas (incidence was not calculated) with a lower burden overall (17/19 studied countries), while the United States had the highest level of burden and 3rd largest prevalence.[78] Of note Canada which began its immunization program in 2000 (second dose 2011) had the second highest burden and prevalence rates.[78] Puerto Rico was not studied. The review only looked at adults 18 years of age and above so was missing pediatric data which again could have demonstrated more changes in migraine-related disability from the alterations in chickenpox rates. From the GBD study 2023, Uruguay had a stable migraine-related burden from 1990–2023 possibly reflecting later initiation of a second vaccine dose, while Puerto Rico was not part of the headache analysis.[79] It is probably too early to decipher if globally the vaccine programs will alter migraine epidemiology as they started on average much later than in the United States.[75] Since 1990, however, migraine burden worldwide as per GBD studies has worsened over time and more so in medium to high sociodemographic index regions, while staying relatively stable in low sociodemographic index countries.[4] This sounds counterintuitive as higher socioeconomic regions should have more access to healthcare at baseline and new migraine acute and preventive medications. The presence of chickenpox immunization programs in wealthier nations and lack of them in poorer countries could be one variable of many helping to explain this paradoxical trend.

Is it the elimination of chickenpox or the vaccine?

At present it is not possible to state if the recent changes in migraine epidemiology are related to the varicella vaccine programs but if there is an association then one must ask whether the reduction in chickenpox incidence or the vaccine itself is associated with these changes. In essence with the current immunizations, humankind is still being "infected with VZV" but it differs from the infection with the wild-type strain. Children are being exposed to the live attenuated virus at typically a younger age than the natural infection and in some nations with the highest immunization rates, two exposures are being given at a presumed muted immune reaction rather than the one major infection that causes a dramatic immune response and forever immune protection.[38] In addition, it has been shown that the live attenuated vaccine virus can set up a latent infection in sensory ganglia but it is not known if it is different from what occurs with the wild-type strain (how much virus infects and if there is a different intensity of cell-mediated immune surveillance).[38] This cause-and-effect question will certainly need further study.

Clinical practice consequences

If migraine is becoming more disabling and more frequent with the varicella immunization programs, then a distinct preventive strategy may need to be established for this population. This could entail starting preventive agents earlier in vaccinated children with a family history of migraine to help guard against migraine chronification and loss of school and family time. The vaccinated population could also be studied for specific preventive agents that are more effective in a chickenpox negative/immunization positive group.

Future directions

Establishing that chickenpox was necessary for migraine to exist is an intriguing hypothesis, but difficult to prove as almost every human in history has had chickenpox. Because the proposed validation parameters are broad, future studies could be converted into testable, falsifiable predictions, including prospective epidemiological studies, VZV-serostatus/exposure analyses, longitudinal migraine incidence, biomarkers of VZV activity, genetic interaction studies, and comparisons between vaccinated and unvaccinated populations.

Specific studies could include:

1. Follow individuals with a family history of migraine and migraine susceptibility genes who did not have chickenpox to determine whether they develop migraine. More informative would be twin evaluations with one twin having chickenpox while the other did not. However, it is very hard if not nearly impossible to find these patients in unvaccinated countries.
2. Look for VZV DNA in the trigeminal ganglia of early humans who underwent trepanation. The earliest report of this procedure is around 11,000 BCE but it is not possible to assume it was absolutely done for headaches and even if it was, we could not prove the patient had migraine as there are no medical writings from this time period.[30] Also, we could not prove if

non-trepanation patients did or did not have migraine if they were VZV DNA negative.

3. Testing whether the live attenuated VZV vaccine can cause migraine is more feasible in the time of immunization but if there has been an evolutionary change to the trigeminal system from the initial varicella infections in early humans it may no longer matter whether VZV is present or not as the system could possibly trigger itself with the correct exposures or maybe any herpesvirus infection could now activate the system and we are not immunizing against these other ubiquitous viruses.
4. Soon there may be a messenger RNA varicella vaccine for chickenpox. This is currently being tested for herpes zoster immunization.[80] This type of vaccine would eliminate the need for live attenuated viral infection. Assessing what happens to migraine epidemiology with messenger RNA vaccines could help test whether chickenpox triggers migraine at least in modern humans.
5. Future studies could stratify individuals with migraine into patients with versus without a history of chickenpox and determine whether they respond differently to medications, have different connectivity issues on functional MRI, or have different cytokine and neuropeptide profiles.
6. We can look at special populations like status migrainosus and note if this is during periods of latent VZV reactivation (not fully as with zoster but subclinical). This could also lead to new antiviral treatment protocols for status migrainosus.
7. Consider the use of antiviral medications as preventive agents for disabling migraine. There are case reports of their use in migraine, and they have already shown efficacy in other headache disorders such as NDPH.[63,81] However, as antivirals have anti-inflammatory/anticytokine activity, their efficacy does not prove a virus-modulating effect.[82]

Limitations

The coexistence of VZV and migraine, their evolutionary timing, and shared neuroinflammatory pathways do not absolutely demonstrate that one caused the other. Several limitations to the proposed hypothesis and validation include: 1) The association between chickenpox and migraine could reflect a causal temporal relationship supported by biological plausibility, reverse causation in which migraine vulnerability increases VZV susceptibility, or shared genetic susceptibility without a direct influence of either condition on the other. Another possibility is that both are influenced by hypothalamic mechanisms reflected in circadian or seasonal periodicity, without a causal relationship. In addition, an environmental association in which migraine activators such as barometric pressure changes or extreme sunlight could have driven early humans to congregate in closed spaces to avoid these exposures, thereby promoting horizontal spread of VZV without the infection being the origin of migraine; 2) A central premise of the proposed hypothesis is that VZV infection may have led to the same neuroinflammatory cascade as seen in migraine. Thus, chickenpox primed the system in susceptible early humans to produce this chronic condition if the correct environmental exposures were present. The issue, however, is that shared cytokines or inflammatory mediators alone are insufficient to establish a direct mechanistic link. This needs further study and could support the proposed hypothesis if neuroinflammatory markers could be evaluated in early humans whose migraine and chickenpox status was known; 3) It may be inferred based on the cytokines and neurotransmitters released during acute VZV infection and other non-inflammatory linkages suggested above that CSD, cortical excitation and hypothalamic alterations could ensue after chickenpox to contribute to the genesis of migraine but there is no direct evidence at present that these issues are generated after VZV infection; 4) Part of the proposed hypothesis is based on the assumption that migraine provides an evolutionary advantage to affected individuals. This is a controversial topic as this may have only been essential in early humans without any effect on present-day civilization or there may have been no evolutionary advantage because persistence of a phenotype does not necessarily demonstrate positive selection; 5) The assumptions that the VZV strains infecting early humans were more virulent and that virtually all early humans were infected lack direct supporting evidence; 6) the genetic evidence involving *TRPM8* and the rs10166942 variant represents a speculative extrapolation; and 7) the proposed relationship between VZV vaccination and changing migraine epidemiology requires stronger empirical support. There are multiple variables that could lead to worsening migraine burden and alterations in incidence and prevalence, including demographic, diagnostic, environmental, and healthcare-related factors and thus it is not possible to interpret what is being reported in the USA and globally as evidence for the proposed hypothesis without appropriate comparative data.

Conclusions

Based on the proposed hypothesis, chickenpox may have contributed to the evolution of migraine susceptibility in early humans, and without VZV infection, the evolution of migraine as we know it may have been different. Whether VZV is still required to trigger migraine in modern humans requires further study. If rigorous comparative studies confirm changes in migraine epidemiology associated with reduced chickenpox incidence after immunization, the hypothesis would gain support. Because the strength of our supporting evidence may be overestimated and much of the evidence is indirect or inferential in nature, further study to validate the proposed hypothesis is necessary.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Author contributions

Hypothesis conceptualization (TDR, EMR, LER), background

research (TDR, EMR, LER), table and figure preparation (TDR, EMR, LER), manuscript drafting (TDR), critical revision of the manuscript (TDR, EMR, LER). All authors edited and revised the paper for important content. All authors approved the final version of the paper. TDR agrees to be accountable for all aspects of the work by ensuring that questions relating to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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