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Theories on Varicella Zoster Virus Reactivation Based on Shingles Patterns

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Abstract

Herpes zoster, a disease also known as shingles or as zoster, infects the sensory nerve ganglion and the peripheral nerve and its branches, resulting in pain to the affected dermatomes. Infection results from reactivation of the varicella-zoster virus, the same virus which causes varicella, or chickenpox. The varicella-zoster virus usually causes chickenpox to its host at an early age and then withdraws to the dorsal root ganglia where it enters a latency stage. The virus may reemerge at any time and infect its host with shingles. As shingles is most common in ages 50 and above, it is assumed that cell-mediated immunity plays a role in suppressing the virus, and, therefore, a decline in this immunity allows the virus to reemerge from latency. Shingles also appears to be more common in temperate regions than in tropical regions, leading to a suggestion that certain genotypes of the varicella-zoster virus are more prone to reactivation than others. Decreased herpes zoster incidence in the African American population and the detection of increased presence of the ATA and GCC haplotypes in herpes zoster patients may point to a genetic predisposition to reactivation of varicella-zoster virus. Evidence of increased female shingles incidence has lead to numerous hypotheses, some of which may shed some light on the mechanism of varicella-zoster reactivation, a phenomenon which is still poorly understood.

Introduction

"Chicken pox is most commonly an annoying illness lasting three to seven days, and happily never seen again" (qtd. in Link 2005). This statement is by and large true about the actual chickenpox illness; in response to a chickenpox disease, the body builds immunity against future occurrences, and rarely does a second case of chickenpox occur. However, the virus which caused the chickenpox may be seen again; it may resurface as a disease called shingles after years of lying dormant.

Chickenpox, the popular name for varicella, was a common childhood rash until the varicella vaccine was licensed for use in the United States in 1995. Prior to the introduction of the varicella vaccine, over 90% of Americans contracted chickenpox by age 15 (Chickenpox 2013). Chickenpox symptoms typically last up to seven days (Simon 2012). However, even after recovery from chickenpox, the causative agent—varicella-zoster virus (VZV)—remains dormant inside the body in sensory nerves. Reactivation of the virus later in life results in shingles, or herpes zoster, and presents differently than its predecessor. Chickenpox appears as an itchy rash and blisters all over the body, and shingles appears as a blistery rash restricted to one side of the body (Figures 1 and 2). While chickenpox is generally considered a mild, unpleasant disease and is short lived, shingles is a more severe, painful disease which can have lasting effects. Generally, shingles symptoms clear in seven to ten days; however, it is not uncommon for it to take as long as a month to clear. The most common debilitating complication related to shingles is postherpetic neuralgia (PHN), defined as pain that persists longer than a month after the onset of shingles and lasts at least 90 days (Sampathkumar et al. 2009). The risk for PHN can reach 25-50% for shingles patients over the age of 50 and up 75% for patients over the age of 70 (Giménez-Milà et al. 2014). Other complications that may arise due to shingles include zoster ophthalmicus (reactivation of VZV in the trigeminal ganglia involving the ophthalmic division of the nerve, potentially damaging the eye and surrounding structures), bacterial superinfections, and neurological manifestations such as meningitis, encephalitis, myelitis, and complex regional pain syndromes I and II (Studahl et al. 2013 and Giménez-Milà et al. 2014).

Methods

In researching the background of varicella and herpes zoster, particularly theories regarding the reactivation of varicella-zoster virus, articles were gathered using various databases of scientific literature. These include PubMed, a service of the United States government, and various databases of health science journals made available through access to the Touro College and Ursuline College libraries.

Pathogenesis

Varicella zoster virus, the causative agent of varicella (or chickenpox), is a member of the herpesvirus family and alphaherpesvirus subclass. After the primary varicella infection, VZV withdraws to the dorsal root ganglia and trigeminal ganglia where it remains latent. In fact, VZV in its latent stage can be found in multiple ganglia along the entire neuraxis (Liesegang 1999). It may remain dormant for the remainder of the life of its host, never causing any viral symptoms, or it may reactivate at any time as herpes zoster (HZ), more commonly known as shingles (Figure 3). However, according to Greg Bennett (qtd. in Polansky 2013), even during the latency period, which may last the entire lifetime of its host, VZV does not

Figure 1:
Chickenpox appears as an itchy rash and blisters all over the body. Source: Chickenpox Photos 2013

Figure 2:
Shingles appears as a blistery rash restricted to one side of the body. Source: Shingles Pictures 2014

remain inactive; transcription of the VZV has been detected even during this period. Reverse transcription polymerase chain reaction has identified multiple VZV transcripts in latently infected human ganglia (Baird et al. 2013). "Thus," claims Bennet, "the idea that the virus is inactive and presents no risk during the so-called inactive period is a misconception. Rather, the latent viruses are active and can be dangerous."

The dermatological signs (i.e. rash and blisters) of herpes zoster are similar in their centripetal distribution to dermatological signs of varicella (Figure 4). This is suggestive that during primary varicella infection, the virus (VZV) spreads from infected skin cells to sensory nerve endings and then to the ganglia where it remains dormant. Subsequently, when VZV reactivates, it appears with the same centripetal distribution (Liesegang 1999). However, writes Liesegang, despite the similar dermatological distribution, it does not necessarily have to be so. It may be that the ganglia are directly infected hematogenously during the viremic phase of the initial varicella infection, and the path VZV takes when it reactivates as herpes zoster is simply indicative of the ganglia most exposed to reactivation stimuli.
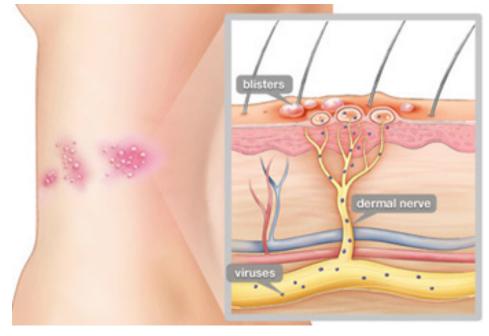

Figure 3:
The varicella zoster virus is the causative agent for chickenpox and shingles. After chickenpox, the virus never goes away. Instead, it settles in nerve cells and may reactivate years later, causing shingles, also called herpes zoster. Source: Smith 2014
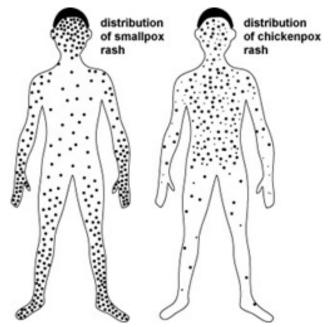
Figure 4:
The chickenpox rash exhibits centripetal distribution, meaning that the greatest concentration of lesions is on the trunk with fewer on distal extremities. This is in contrast to the smallpox rash which exhibits centrifugal distribution, meaning that the greatest concentration of lesions is on the face and extremities with fewer on the trunk. Source: Antipuesto 2008

Epidemiology

Regardless of the path taken by VZV from initial varicella infection through latency and finally reactivation as herpes zoster, the cause of VZV reactivation remains unknown. There are numerous hypotheses as to what causes reactivation of VZV, although there is no concrete evidence supporting any one hypothesis and certainly no consensus among researchers. It is quite clear, however, that risk of herpes zoster increases with age. This is widely attributed to the decline of cell-mediated immunity (CMI) that progresses with aging. It is assumed that the dormant VZV is held in check by the cell-mediated immunity, not humoral immunity, so when CMI declines, the virus can flare up. Humoral immunity is assumed not to play a role in suppressing VZV, for herpes zoster has been shown to occur even in the presence of high levels of antibody titer, and antibody titer is a measure of humoral activity (Liesegang 1999).

Genetic Correlation

Philip S. Rice (2011) suggests a genetic correlation as governing the latency and reactivation of herpes zoster virus. He hypothesizes that exposure to the sun, or more particularly to ultra-violet radiation (UVR), plays a significant role in determining the genotype of the VZV, and, thus, the virus has evolved into different genotypes based on climate. He builds his hypothesis on the fact that incidence of varicella is significantly lower in tropical regions than in temperate regions and that, even in temperate regions, varicella incidence is at its lowest in the summer. (In regions near the equator, i.e. tropical regions, the sun's rays arrive almost perpendicular to them, thus higher levels of radiation. Near the poles, i.e. temperate regions, the angle of the sun's rays spreads them out over a much greater area, providing less energy per unit of area (Raven et al. 2005).) He posits that in the tropics, the high levels of ultra-violet radiation may inactivate varicella virus in the vesicular fluid either before or after rupture of the vesicles. According to Asano et al. (1999), vesicular virus contributes more to the spread of the virus than the shedding of the virus from the respiratory tract. Consequently, in the tropics, transmission of varicella virus is significantly diminished due to ultra-violet radiation. As early humans lived in Africa—a tropical region— the virus evolved into a genotype resistant to ultra-violet radiation as a survival strategy. When humankind spread to temperate regions, however, the virus shed its selective advantage of UVR resistance. However, as an evolutionary tradeoff for its lost advantage and, thus, reduced transmissibility (during the summer months when UVR is strongest), the virus increased its propensity to reactivate as herpes zoster in order to ensure its continued survival in temperate regions. Accordingly, the temperate genotype of VZV is prone to reactivation while the tropical genotype is not (except in severely immunosuppressed individuals). This explains why data of herpes zoster incidence in tropical countries is virtually absent. Rice, thus, suggests that the same mechanism responsible for UVR resistance in tropical VZV genotypes may also play a role in the latency and reactivation of temperate genotypes.

Quinlivan et al. (2013) also mention findings of various genotypes of VZV according to country. They write that VZV genotyping has identified five clades (a clade is a group consisting of an ancestor and all its descendants) of which clades 1 and 3 predominate in Europe, clade 2 in Japan, and clades 4 and 5 in Asia and Africa. Liesegang (1999) also notes the significant variation of VZV between tropical and temperate regions and insists that it must be due to agent specificity.

A point one can take issue with and not addressed by Rice is that if the tropical genotype has acquired UVR resistance in order to avoid inactivation by ultra-violet radiation, then why is incidence of varicella lower in tropical regions than in temperate regions; shouldn't the tropical genotype be able to thrive in constant sunlight just as well as the temperate genotype does in decreased sunlight? The answer to this question may lie in that varicella is easily spread by respiratory route via airborne transmission, and this form of transmission is aided by winter weather. In addition to increased coughing during the winter months and the tendency to remain indoors due to the cold temperatures outside, the cold, wet weather may aid the survival of the virus outside a host (Zak-Prelich et al. 2002). In the tropics, despite the advantage of UVR resistance, the virus lacks the advantage of winter weather aiding in spreading it, and this may explain the lower incidence of

varicella there. Although, as Rice quoted from Asano et al. (1999), vesicular virus contributes more to spreading of the virus than does airborne transmission from the respiratory tract, and the tropics have the advantage of vesicular transmission even in presence of ultra-violet radiation, the lack of increased airborne transmission may still be a viable explanation for the significantly lower incidence rate in the tropics.

Another setback to Rice's hypothesis is a suggestion from Gallerani and Manfredini (2000) that ultra-violet radiation might be responsible for increased incidence of herpes zoster in the summer months (in temperate regions) due to its ability to suppress cellular immune response (Figure 5). When immunity to VZV is reduced, the latent virus is then able to reactivate as herpes zoster. This would suggest that ultra-violet radiation aids in virus activation, while Rice suggests that ultra-violet radiation is an inactivator of VZV. However, this is easily answered by the different methods of activation in both diseases. Varicella is transmitted from person to person by vesicular route or respiratory route. Thus, because the virus in the vesicles (in the temperate genotype) is inactivated by ultra-violet radiation, spread of the virus is decreased. Herpes zoster, on the other hand, can only develop from reactivation of a latent VZV; it is never transmitted from one person to another (Simon 2012). Reactivation of the latent VZV is largely due to immunosuppression. Thus, ultra-violet radiation does not actually reactivate the virus, it merely suppresses the immunity that is keeping VZV dormant, and this allows VZV to reactivate. In other words, ultra-violet radiation may, in fact, inactivate vesicular varicella virus as Rice posits, and the fact that ultra-violet radiation is also responsible for increased herpes zoster incidence is not contradictory, because ultra-violet radiation does not actually activate herpes zoster.

While Rice suggests that genetic variations in the VZV itself result in prevalence or scarcity of VZV reactivation, others suggest that genetic variations in human subjects may be responsible. Schmader et al. (1998), in a study of communities in North Carolina over a six-year period, found significantly fewer herpes zoster cases among black subjects than among white subjects. To explain this phenomenon, they suggest that decline in cellular immunity due to aging may be less in black people than in white people, although they offer no explanation as to why. However Thomas and Hall (2004) take a novel approach in explaining why this may be so. They suggest that a less significant decline in cellular immunity among aging black subjects may be due to differential survival, or natural selection. "In populations with higher mortality rates, those who survive to old age may have robust immune systems (and therefore lower susceptibility to zoster)," they write. (They may be referring to the high mortality rate of even young children in Africa. They may also be referring to the increased mortality rate, even in the US, among African American children [Infant Mortality and African Americans 2013] Another approach Thomas and Hall take is that it may be caused by genetics; genetic differences between black subjects and white subjects may result in decreased or increased incidence of VZV reactivation, respectively. This approach suggests that genetic variations among the human race may be behind the propensity toward VZV reactivation.

One can also argue that the difference in herpes zoster incidence between black subjects and white subjects is due to variations of the VZV genotypes rather than genetic variations among humans, based on the findings of five different clades of VZV, with clade 5 predominant in Africa and Asia (Quinlivan et al. 2013). This argument adds credence to Rice's position that tropical VZV genotypes are less prone to reactivation than temperate genotypes. Although
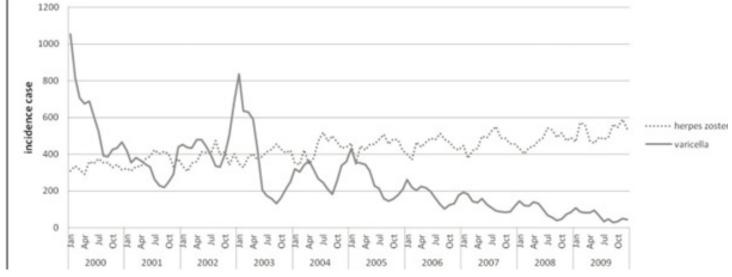
Figure 5:
Annual trend of monthly incident cases of herpes zoster and varicella in 2000–2009. Notice that herpes zoster spikes during the warmer months. Source: Wu et al. 2013

Rice writes that immigration from Africa to temperate regions gave way to the temperate VZV genotype, such a transition might take some time, and recent immigrants and their offspring may still harbor the tropical genotype. This is especially plausible when taking into account that the reactivating strain of VZV is identical to the strain that had caused the primary varicella infection (Sengupta et al. 2007). Thus, the tropical VZV genotype can persist and still be widespread in aging African American populations long after immigration from Africa.

Another genetic correlation is suggested Haanpää et al. (2002). They suggest that susceptibility to herpes zoster may be genetically predetermined. Interleukin-10 (IL-10) is an anti-inflammatory cytokine; it downregulates the production of the proinflammatory cytokines, thus decreasing cell-mediated immunity. The promoter region of the gene for IL-10 is polymorphic, producing three different haplotypes (combinations of DNA sequences on one chromosome that are inherited together): GCC, ACC and ATA. Blood samples taken from herpes zoster patients and from controls not infected with herpes zoster showed a significantly higher presence of the ATA haplotype in the blood of herpes zoster patients. This suggests that IL-10, its presence detected by detection of the ATA haplotype, may play a role in VZV reactivation. The explanation of this is that VZV reactivation is largely due to decreased cell-mediated immunity, and this immunity is decreased by IL-10. Consequently, inheritance of the ATA haplotype may predispose one to herpes zoster. This idea is echoed by Cho (2007) who writes that in Korea, the GCC haplotype is significantly higher in herpes zoster patients than in controls not infected with herpes zoster, and this may point to the role of IL-10 in reactivation of VZV and a possible genetic predisposition to herpes zoster. Cho attributes the differences in increased haplotype findings between the previous study conducted in Finland and his own study conducted in Korea simply to ethnic differences between European and Asian populations. Their differences notwithstanding, the ideas of both studies are the same—that IL-10 may be a factor in VZV reactivation leading to herpes zoster, and genetic inheritance of a specific haplotype of the IL-10 promoter gene may predispose carriers to herpes zoster. This suggestion, too, assumes genetic variations in human hosts, rather than genetic variations in the VZV itself, to be behind increased or decreased incidence of herpes zoster.

Gender Correlation

Numerous studies and trials report a higher incidence of herpes zoster in females than in males (Figure 6). In one such report, Fleming et al. (2004) investigate the gender differences in incidence of herpes zoster by dividing patients into age groups: 0-14, 15-24, 25-44, 45-64, 65-74, and 75 and older. Over the eight-year study, there were 14,532 cases of herpes zoster, of which 59.3% were female patients and 40.7% male patients. Female herpes zoster incidence exceeded males in all age groups except for the

15-24 age group in which the rates were almost equal for both genders. The greatest female risk appeared in the 45-64 age group followed by the 0-14 age group.

There are numerous attempts to determine what is behind the female predisposition to herpes zoster incidence. Possibly, resolving what is behind increased female incidence can shed some light on the mechanism of VZV reactivation in general.

Various reasons for the female excess are given. One suggestion is that there are more herpes zoster cases among females due to their longevity; because women live longer than men, there are more occasions for them to contract herpes zoster. Fleming et al. (2004) write, however, that their analysis disproves the theory, for it indicates female excess in nearly all age groups. If increased female incidence were due to female longevity alone, an increase in female incidence would only be evident in older age groups—age groups in which females generally outlive males. Another suggestion given is that women tend to seek medical advice more readily than men, and, thus, there are more reported cases of females with herpes zoster than of males (Thomas and Hall 2004). This
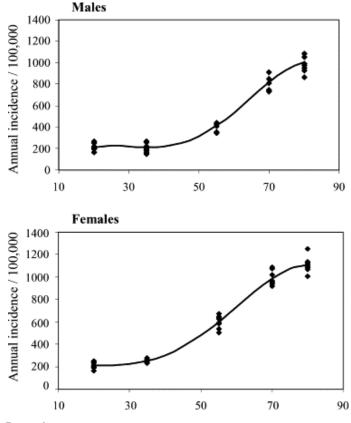

Figure 6:

Annual incidence per 100,000 of shingles by age group and gender in years 1994–2001 with superimposed regression line. Source: Chapman et al. 2003

would suggest that, in truth, females are not more susceptible to herpes zoster than males; it only appears that there is higher herpes zoster incidence in females, because they are quicker to see a doctor for symptoms, and, thus there are more female herpes zoster patients recorded in the system. (In one case, a 60 year old man waited ten days before making an appointment to see a doctor despite pain rated 6 out of 10 on the pain scale and a rash which appeared within a week of the onset of the pain! (Martić 2014)) This theory, however, would seem to be disproved by the data provided by Fleming et al. (2004) which finds that in the age group of 15-24, female rates of herpes zoster did not exceed male rates and by data provided by Ragozzino et al. (1982) which actually finds lower incidence of herpes zoster in females aged 35-44 than in males of the same age group.

A more sophisticated approach to explain the increased herpes zoster incidence in females is taken by Fleming et al. (2004). They suggest that there may be a true gender difference in the way the body responds to reactivation of a latent virus. They base this theory on the fact that there is also a significant female excess in incidence of herpes simplex virus, another member of the herpesvirus family and alphaherpesvirus subclass, which is also a virus that reactivates after a long latency period in ganglionic tissue. Although they do not specify what might be behind the difference in reactivation response based on gender, the suggestion of Studahl et al. (2013) may shed some light on it. Studahl et al. suggest that the difference in herpes zoster incidence between genders may be due to hormonal differences between men and women. It may be the hormonal differences between the genders that affect the way the body responds to virus reactivation.

In a similar vein, the menopause transition period females go through is also suspected to be responsible for increased female herpes zoster incidence due to hormonal changes to their immune response (Saunders 2014). This theory is supported by the aforementioned findings of Fleming at al. that females aged 15-24 did not exceed males in herpes zoster incidence and the findings of Ragozzino et al. that females aged 35-44 actually have lower herpes zoster incidence than males, for they have not yet reached the menopausal stage. This theory, however, fails to address increased herpes zoster incidence in females past the menopausal stage, when hormone levels are static.

It should be pointed out that, even according to hypotheses correlating increased herpes zoster incidence in females with their hormones or menopausal shifts, they do not claim these to be the sole causes of VZV reactivation, for herpes zoster occurs in males too, albeit not as prevalent as in females. They simply suggest that among other factors influencing VZV activity, these contribute on greater levels to its reactivation. Thus, while even those lacking these factors may get herpes zoster, those that have these factors are at a greater risk of getting herpes zoster.

Still, there does not seem to be a clear understanding as to the exact role hormones play in increasing herpes zoster incidence, and no explanation has been offered as to which hormones might be involved. Are female hormones responsible for the increased herpes zoster risk in females, or are male hormones responsible for decreased herpes zoster risk in males? After all, males have a higher risk for a severe case of chickenpox than females (Simon 2013). Maybe this points to some type of male hormone influence on VZV. On the other hand, there is more fluctuation in female herpes zoster incidence between the different age groups, suggesting that female hormones more likely play a role in VZV reactivation and that fluctuation in their levels contributes to an increase or decrease in herpes zoster incidence. In addition, as previously mentioned, the latent VZV is held dormant by cell-mediated immunity, not humoral immunity. In pregnant women, "the fetoplacental unit redirects maternal immunity away from cell-mediated immunity towards enhanced humoral responsiveness" (Wegmann et al. 1993). This would lead to the assumption that women are at a high risk for VZV reactivation during pregnancy. This, however, is not the case. According to Simon (2012), herpes zoster is extremely rare in pregnant women. While this phenomenon is not well understood, it does strengthen the case for female hormone involvement in increased female incidence as opposed to male hormone involvement in decreased male incidence.

Conclusion

While the particular method of VZV reactivation remains unclear, numerous hypotheses are offered based on various presentation patterns of herpes zoster. Some suggest that genetics plays a role. One such study focuses on regions where herpes zoster is or is not prevalent and suggests that VZV genotypes differ according to region with temperate genotypes prone to VZV reactivation while tropical genotypes are not. Another study focuses on the decreased herpes zoster incidence among African Americans and suggests that genetic differences between white subjects and subjects of color may increase or decrease susceptibility to VZV reactivation. Yet another study suggests that inheritance of certain genetic haplotypes may predispose one to herpes zoster. Others focus on the difference in herpes zoster incidence by gender. Instead of citing genetics as possibly influencing increased female incidence, some suggest that female hormones may be largely responsible. Similarly, others suggest that menopausal instability may prompt VZV reactivation.

"The peculiar pathogenetic mechanism of herpes zoster infection, its capacity to migrate after the primary infection (varicella) to the dorsal root ganglia and remain silent throughout life, makes it somewhat difficult to put forward convincing hypothetical explanations" (Gallerani and Manfredini 2000). Nonetheless, each of these observations of herpes zoster patterns and diverse suggestions as to what is behind the patterns and what they mean sheds some light on the mechanism or mechanisms of VZV reactivation. Each insight offers a unique angle at which the phenomenon of VZV reactivation can be further studied.

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