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Literature Review

Human Herpes Varicella Zoster: An Appraisal, Pathogenesis and Therapy

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Abstract

Objective: This appraisal describes the pathogenesis and presentations of primary and secondary Human Herpes Viruses particularly focusing on the Shingles Human Herpes Virus, Varicella Zoster (HHVZ).

Design: Pertinent literature on management and treatment of Human Herpes Varicella Zoster Viruses were reviewed.

Results: Primary exposure HHVZ infection manifests as Chicken-pox mainly in children. Subsequently HHVZ settles into sensory ganglions, where immunity restrains its' activity. As age reduces immunity recrudescence of HHVZ is stimulated, and infected persons manifest crops of painful vesicles. A reliable prophylactic vaccine against HHVZ exists and antiviral medications effectively moderates symptoms and manifestations.

Conclusion: Recrudescence of HHSVZ remains obscure but successful prevention resides in vaccines. Common stigmata locations are indicated and anti-virals for HHSVZ are tabled.

Keywords: *Chickenpox; Herpes; Singles; Varicella; Virus; Zoster*

Abbreviations

EBV: Epstein Barr Virus; HHSV: Human Herpes Simplex Virus; HHVZ: Human Herpes Virus Zoster; HIV: Human Immunodeficiency Virus; HPV: Human Papilloma Virus

Highlights

Herpes Varicella Zoster pathogenesis is deconstructed, recognition, management and treatment are outlined.

Background and Introduction

Herpesviridae are made up by structurally different complex viruses consisting of double stranded DNA genomes. There are eight acknowledged types of human Herpes Viruses: Herpes simplex types 1 and 2 (HHSV-1 and HHSV-2); Varicella zoster (HHVZ, or HHSV-3); Epstein-Barr Virus (EBV or HHSV4); Human cytomegalovirus HCVM, or HSV 5); Human herpes virus 6 (HHSV-6); Human herpes virus 7

(HHSV-7); and Human herpes virus 8 (HHSV-8). These eight are grouped into three subfamilies: the alpha-herpesviruses that includes HHSV-1, HHSV-2 and HHSV-3 (HHVZ). These invade rapidly, reproduce and establish themselves as dormant viruses in sensory ganglia. The beta- and gamma-herpesviruses are lymphotropic. These three groups (Alpha and Beta-with-Gamma groups) are distinguished from each other and on the basis of their genomes-organization and patterns of replication [1].

Human Herpes Varicella-zoster virus (HHVZ) is one of the Human alpha-herpesvirus group, prevalent globally, and is the cause of the exanthemata disease Chickenpox (Varicella) in children, and Shingles (Herpes zoster) later in life. Chickenpox is a ubiquitous, common childhood disease (mainly before puberty but may occur up to age 25) with widespread scattered vesicular lesions of the skin, accompanied by pyrexia, viremia, and malaise [1-3].

Aim of the Study

This appraisal reviews Human Herpes Virus infections with specific emphasis on Human Herpes Varicella Zoster (HHVZ; Shingles).

Human herpes viruses and pathogenesis of infection

Varicella infections are ubiquitous, spread worldwide and are most prevalent in heavily populated metropolitan societies. Before vaccines were introduced, the incidence of Varicella infection occurred in children, with 50% of most populations being infected by 5 years of age and 90% by 12 years. By 2022, the introduction of voluntary vaccinations against Varicella, has significantly reduced these rates of infection. Varicella is not a uniquely human disease as it may infect Simian species like monkeys, baboons and the hominid apes, but Varicella is one of the most readily infectious of human illnesses [4]. Varicella spread is by direct contact with fluid from the lesions or through any airborne spread from the respiratory tract. Transmitted infection in human households can be close to 90% [4,5].

A characteristic of the alpha Herpes viruses, (Human Herpes Simplex Virus type 1 and Human-Herpes Simplex Virus Type 2: HHVS-1 and HHVS-2) is to establish latency sensory dorsal root ganglia cells, after the primary infection. HHSV-1 and HHSV-2 are responsible for Herpes labialis and facial Herpes, and genital Herpes respectively [6-9].

The HHV-Zoster virion consists of a nucleocapsid surrounding a core that contains the linear, double-stranded DNA genome; a protein tegument separates the capsid from the lipid envelope, which incorporates the major viral glycoproteins. HHV-Zoster exists globally but is most prevalent in temperate climates. Primary HHV-Zoster infection induces some form of immunity with antibodies in the form of immunoglobulin G (IgG), IgM, and IgA antibodies, which may bind to many classes of viral proteins. In healthy patients with primary or recurrent HHV-Zoster infection, production of specific HHV-Zoster viral cellular-immunity is essential for constraining viral replication. HHV-Zoster will flare up with reduced immunity, like in old age, or with compromised immunity like in HIV infected or those are immunosuppressed post organ transplant. Laboratory confirmation using polymerase chain reaction (PCR) for diagnosis of Varicella or HHV-Zoster is possible by detecting viral proteins or DNA and is essential to determine, which indicates the need for prescribing antiviral therapy [3,5,10,11].

The definitive symptom of Chickenpox is the appearance of a widespread itchy skin, followed by a vesicular rash that not only erupts all over the body, but also in the mucous membranes and upper respiratory tract, including the eyes, mouth, face, scalp, and genitals. The rash generally starts on the torso and proximal limbs, then generally spreads distally to the face, genitalia, and distal limbs. The fluid-filled vesicles erupt repeatedly in "crops", so that various stages of the Varicella infection are present as the initial, florid, and older crusted lesions, all of which may manifest simultaneously. Clinically, common early symptoms include slightly elevated fever followed by mild malaise with a runny nose, and headache. Before infection manifests the latent period is 10 to 21 days after which symptoms appear. The lesions persist for 10 to 14 days, but Varicella is most contagious just before, during or after the first or second day after the eruption of the rash with vesicle formation. Small ulcers form which then transform to crusts. An infected person is capable of transmitting virions

until the crusty-scab lesions fall off. The Varicella stigmata vary widely; it may be minor, with only a few eruptions, to extremely serious morbidity with widespread body-rashes, high temperature and debilitating malaise. Adults manifest more severe forms of the infection especially with depressed immunity, with higher risks of developing viral meningo-encephalitis [8,9].

After the initial Varicella illness, the HHV-Zoster travels centripetally to the sensory nerve ganglia where it resides in a latent state. Should an activating stimulus provoke the HHV-Zoster [HHVZ], the reactivated HHV-Zoster virions travel by centrifugal movement along the sensory axons nerve, to the nerves ending where characteristic eruptions manifest as vesicular rash. The rash is demarcated by the area innervated by the infected sensory nerve. HHVZ on the torso, typically invades a dermatome, which is the cutaneous area of skin supplied by one spinal nerve. It may also invade a cranial sensory nerve, like the Facial (VII) or Glossopharyngeal (IX Cranial Nerve). Zoster infection is often unilateral. When the facial VII cranial nerve is involved, it is considered a medical emergency as it carries a high risk of causing permanent hearing loss and facial weakness, which can impact the eye and vision. Human Herpes Varicella Zoster (HHV-Z) infection happens later in life as and is also known as shingles [2,9-11].

Complications of HHV

HHV-Zoster morbidity embraces a whole host of pathologies. These include secondary bacterial infections: Varicella increases the susceptibility to severe invasive group A streptococcal infection in previously healthy children by 40- to 60-fold risk. Infections may occur in skin and soft tissues including otitis media, bacteremia, pneumonia, osteomyelitis, septic arthritis, endocarditis, necrotizing fasciitis, toxic shock-like syndrome, hepatitis, thrombocytopenia, cerebellar ataxia, stroke and encephalitis. Serious complications arise among immunocompromised people, especially in adolescents and adults who have high rates of morbidity and mortality from pneumonia, and encephalitis [12,13].

Concomitant Herpes infection can also act as a strong co-factor in the development of severe generalized periodontitis in children and adults [14-17]. Latent Herpes viral infection also manifests as Herpes gladiatorum [42,43].

Shingles manifests as a painful vesicular skin rash that usually develops on one side of face or torso. The rash outlines the sensory nerve innervation of the area affected. The initial eruption is a rash of small vesicles that typically burst over 7 to 10 days, form a crusty scab and clears up within 2 to 4 weeks. Many describe the associated pain as an intense ongoing burning sensation. In some people the pain persists and lasts longer for months or even years after the rash clears up. This chronic pain is termed postherpetic neuralgia (PHN), and it is the most frequent and common complication of shingles. The prevalence of shingles and PHN increases with age.

Herpes in pregnancy

The risk of neonatal infection varies from 30% to 50% for HSV infections with late onset in pregnancy (last trimester), whereas early pregnancy infection carries a lower risk, with a prevalence at about 1 - 2% risk of infection. Congenital HHV-Zoster infection varicella syndrome is rare but may take hold between the 13th or after the 20th week of gestation. Should primary HHSV infection occurs during late pregnancy, there is not adequate time to develop constraining antibodies to suppress viral replication before labour. Consequently, congenital anomalies from infection may manifest and embraces a wide range of morbidity including low birth weight, ophthalmic abnormalities, skin scarring, limb atrophy, cerebral atrophy, and other anomalies. Mortality is high with one in three affected infants succumbing early by the second year of life. Vertical transmission of HZV from infected mothers to infant results in severe neonatal varicella (up to 30%) morbidity with a high mortality rate for newborns [18]. The vertical transmission and elimination of the virus during birth with other clinical manifestations are significantly reduced by caesarean birth and treatment with acyclovir and/or valacyclovir during pregnancy to term [18,19].

Therapy and management of varicella zoster

Treatment for Herpes Zoster in mainly through prophylaxis. That is, the use of a vaccine or neutralizing constraining antibodies by vaccination, and if not, by use of antiviral drugs (See below). Optimal protection against developing Shingles is by prophylaxis with a Vaccine such as Shingrix by GSK [20,22,23].

An effective vaccine to protect against developing Shingles in senior adults (people over 55 years old) is also available. Prior to 1987, the pre-vaccine era in North America (Canada and USA) had high adult and infant mortality by comparison to the post-vaccination era, starting 1995 to 2000 onwards [20-24].

Use of acyclovir, valacyclovir, and famciclovir antivirals are effective for treatment against HHS-Varicella and HHV-Zoster.

Following is the list of available antiviral medications. These medications have proved effective at constraining and reducing Herpes Viral pathologies when started promptly once the vesicular rash first appears.

Medication	Dose rate	Route
For first outbreak of oral herpes		
Acyclovir	400 mg three times a day for 10 days	Orally
Valacyclovir	2000 mg every twelve hours for one day	Orally
Famciclovir	250 mg three times a day for 7 to 10 days	Orally
For Recurrent infection		
Acyclovir Cream 5% for recurrent herpes labialis (Zovirax)	• 5g apply 4 - 6 times daily for 7 - 10 days	Topical
Acyclovir	• 400 mg three times a day for 5 days • 800 mg twice a day for 5 days • 800 mg three times a day for only two days	Orally
Valacyclovir	2000 every twelve hours for one day	Orally
Famciclovir	1500 mg once a day	Orally

Table 1: *List of antiviral medication [35,36].*

Exact mechanisms for recrudescence of Human Herpes Viruses is complex and remains obscure, but re-awakening and reactivation is frequently caused by stimulating the latent dormant Herpes is by various stressors, reduced immunity and/or a whole host of various physical stimuli. Although HHVZ usually manifests unilaterally, it may be bilateral. Both sexes are equally affected. Crops of skin vesicles may form on the torso (thorax or abdomen), fuse and erupt, leaving behind that crusty exudate which usually heals without scarring. If HHV-Zoster affects the Facial- and auditory nerves. It is called, "the Ramsay Hunt Syndrome," with ipsilateral facial paralysis, which is usually transitory, with herpetic vesicles on the external ear, or tympanic membrane which may or may not be associated with tinnitus, vertigo, and hearing disorders. The affected area remains extremely painful, as even after healing, there is marked post-Herpetic painful neuralgia (PHN), which may persist for months. It is sometimes called geniculate neuralgia or oticus. The prevalence of HHV-Zoster manifestly increases with advancing age and/or immuno-suppression [25,26].

Vaccines

Previously a live attenuated varicella vaccine (Merck Zostavax strain) was recommended for routine immunization, but from 2022 a more effective vaccine (Shingrix) for senior adults (people over 55 years old) is available [20-23]. Initially a live shingles vaccine called

(Zostavax) was available, but due to unpredictable outcomes, as of November 18, 2020, Zostavax is no longer recommended for use in the United States. An improved recombinant HHV-Zoster, Shingles vaccine is available and known as "Shingrix" [29-33].

Shingrix vaccine (GSK)

Figure 1

Shingrix vaccine (GSK) is preferred over Zostavax for the prevention of Zoster and related complications; Shingrix is an effective vaccine imparting protection against HHVZ with 90% efficacy after a four-year follow-up. Shingrix requires two doses with a six month break between the first and second intramuscular injections. Shingrix also reduces the risk of postherpetic neuralgia [32,33].

Zostavax vaccine (Merck Sharp and Dohme Corp. May 2018)

Figure 2

Before (1995) vaccination, HHV-Zoster was ubiquitously and commonly prevalent in entire populations with severe morbidity and mortality deriving from both primary Varicella HHS-Varicella and HHV-Zoster reactivation. Chickenpox in the United States caused about 4 million cases annually, with 10,600 hospitalizations up to 150 deaths. Post HHS-Varicella vaccine approval in 1995, a significant reduc-

tion was evident in morbidity, and mortality from Chickenpox (HHS-Varicella). The Food and Drug Administration approved a HHV-Zoster vaccine, with higher concentrations of the same live attenuated virus used in the primary HHS-Varicella vaccine, for seniors 60 years of age or older. This vaccine significantly inhibits reactivation of the HHV-Zoster and the severe the post herpetic pain experienced by those infected [LT1]. [11]. Zoster vaccine live (Zostavax) is no longer available for use in the United States, as of November 18, 2020 [22,23,32,33].

In 2006 a two-dose vaccine series, was recommended for children and was more effective in preventing break-through disease after a one dose vaccine. Older adults also benefit from the two dose HHV-Varicella vaccine by inducing stronger immune reactions.

HHV-Zoster virions are produced in the cells of the Shingles eruptions. The process of HHVZ replication also produces many cell free virions in the cutaneous skin lesions which are infectious for transmission to other susceptible individuals [32]. Breakthrough infections will be moderated with therapy and has fewer blisters forming, reduces infectivity and reduces pyrexia [33-36].

Since the 1960's Aluminium salts (alum) are used as an adjuvant in vaccines, but its' exact mechanism of action remains obscure. Immune responses and protection have improved with adjuvants like oil-in-water emulsion MF59, which is used in influenza vaccines [37,38]. AS01, which is used in one of the shingles vaccines is also in the licensed malaria vaccine and AS04 is also used in a vaccine against human papillomavirus (HPV) [40,41].

Concluding Remarks

Although HHSV may affect some simian species, HHVZ is regarded as a mainly human disease and among the most readily infectious illnesses. Varicella can be prevented by immunization. The National Advisory Committee on Immunization (NACI) recommends that healthy children 12 months to 12 years of age should receive two doses of varicella-containing vaccine (univalent varicella or MMRV) for primary immunization.

HHVZ infection as Shingles occurs after a latent period from Chickenpox. It is prevalent in the aged and immunocompromised. HHVZ will spread by direct contact with fluid from the lesions or through the airborne aerosol spread from the respiratory tract. Varicella varies in severity from very mild, with just a few spots, to severe, with fever and a widespread rash, but Varicella is often more severe in adults. After the initial varicella illness, HHVZ establishes latency in the sensory nerve ganglia, and can be reactivated later in life as shingles. Complications are more common in adolescents, adults, and immunocompromised people, who have higher rates of pneumonia, encephalitis and death.

Varicella Zoster (HHVZ) as Shingles is a recrudescent viral disease derived from a primary infection of Chickenpox. HHVZ infects mainly adults with compromised immunity. Treatment is mainly with a prophylactic vaccination, and the illness can be moderated by antiviral therapy. Complications of infection can produce serious morbidity with post-herpetic neuralgia.

Authors Statement

The authors have no conflicts of interest to declare.

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