

Research Article

Pathophysiological and Epidemiological Aspects of Herpes Zoster: A Short Review

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Abstract

Varicella-zoster virus (VZV) causes two distinct diseases, varicella and herpes zoster. Varicella represents the primary form of VZV infection which usually occurs among children. Herpes Zoster (HZ) is caused by endogenous reactivation of latent VZV, and is mainly observed in the elderly and immune compromised individuals. It is characterized by prodromal pain along one or more skin dermatomes and grouped herpetic form vesicles on an erythematous base.

The lack of VZV-specific immune surveillance, abnormalities of host cellular events-induced silencing of VZV gene expression, immune senescence and immune suppression have been implicated in HZ pathogenesis. The HZ incidence increases with advancing age and HZ recurrence is more frequently observed in immune compromised individuals compared to immune competent persons. The zoster vaccine has been shown to reduce the HZ incidence and postherpetic neuralgia by exogenous boosting of VZV-specific immunity.

Keywords: Herpes zoster, VZV, Varicella-zoster virus, Incidence, Immunity, Vaccine

Introduction

Varicella-zoster virus (VZV) is a member of the Herpesviridae family. On the basis of its biological and genomic properties, VZV is classified as a member of the alpha herpesvirus subfamily which also includes herpes simplex virus types 1 and 2 (HSV-1 and -2). More specifically, VZV belongs to the eight-membered group of the human herpesviruses known to infect only humans [1] (Table 1).

VZV is the causative agent of two clinically distinct diseases: varicella (chickenpox) and herpes zoster (shingles). Varicella is the consequence of primary VZV infection in VZV-naïve individuals. It is a common childhood disease, characterized by viremia and scattered vesicular rash with simultaneous presence of skin lesions in all stages of development and installation of the virus in multiple sensory ganglia where latency is life long established [2]. Herpes zoster (HZ), also known as shingles, is an infectious self-limiting disease caused by the endogenous reactivation of latent VZV in the cranial nerve ganglia, dorsal root ganglia or autonomic ganglia in elderly and immunocompromised individuals [3].

Virological Features of VZV

Structure of the VZV genome

VZV virions are pleomorphic and 180–200 nm in diameter [4]. They contain a linear double-stranded DNA molecule of 125,000 bp in length, which encodes at least 71 open reading frames (ORFs) [5,6]

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Received: May 04, 2018; Accepted: May 30, 2018; Published: June 02, 2018

and is enclosed in an icosahedral protein capsid that consists of 162 capsomeres [4,6].

The latter is surrounded by a cover layer consisting of proteins that are involved in the initiation of the viral DNA replication in the infected cells and an outer lipid envelope with embedded glycoproteins. These proteins determine the antigenic properties of the virus, stimulate the immune response, bind to membrane receptors of the host cell and affect the cellular tropism resulting in the onset of the infection [7].

Upon virus invasion in target cells, the viral DNA is released from the capsid into the nucleus of the infected cell where it becomes circular. Three classes of viral genes are expressed: a. immediate-early genes, b. early genes, and c. late genes [1].

Immediate-early genes are expressed within the first hours of the infection and upregulate the transcription of early and late viral genes [4,8].

Early genes expression precedes the DNA replication of the virus. These genes encode proteins essential for DNA replication, including DNA polymerase, nucleotide synthetases, ribonucleotide reductases and kinases, such as thymidine kinase [8].

Late genes encode structural proteins of the viral capsid and glycoproteins, which participate in the virions formation, while their transcription is suppressed by DNA synthesis inhibitors [4].

VZV genome is stable and only one serotype had been described until 1995 [9]. Recently, based on Single Nucleotide Polymorphisms (SNPs), five subtypes of wild type VZV have been identified, including the Oka strain of live attenuated VZV which is contained in the two available varicella and HZ vaccines [10,11].

Biological properties of VZV

VZV has characteristic biological properties including:

i) The tissue tropism in:

- CD3+ T-lymphocytes, including CD4+, CD8+, CD4+CD8+ and CD45RO subpopulations, affecting mainly the tonsils and other lymphoid tissues that comprise the Waldeyer's ring [6].
- Antigen-presenting cells, skin and mucosal epithelial cells, and fibroblasts [1,12].
- Sensory ganglia [1].

HHV-1	Herpes simplex virus 1 (HSV 1)
HHV-2	Herpes simplex virus 2 (HSV 2)
HHV-3	Varicella-herpes zoster virus (VZV)
HHV-4	Epstein-Barr virus (EBV)
HHV-5	Cytomegalovirus (CMV)
HHV-6	Associated with roseola infantum
HHV-7	Associated with pityriasis rosea
HHV-8	Associated with Kaposi's sarcoma

Table 1: Human herpesviruses.

ii) The ability to establish lifelong latency in the cranial sensory and dorsal root ganglia of the host following the primary infection and reactivation in both healthy and immunocompromised individuals [13].

Immunologic abnormalities in VZV infection

VZV infection causes both innate and adaptive immune systems alterations characterized by:

Suppression of the innate immune response in VZV infected cells, leading to interferon- α and - β down-regulation [14].

Induction of the innate immune response in adjacent uninfected cells and interferon α and β production, which inhibit virus replication during the primary infection [8,15].

Activation of natural killer cells, the major source of interferon γ , that promotes the clonal expansion of viral antigen-specific T-cells [16].

VZV-specific IgA, IgM and IgG antibodies production by B-lymphocytes [17], which neutralize the viral particles in the inoculation sites upon re-exposure to the virus. Nevertheless, the VZV-specific antibody production does not affect the occurrence of HZ [8,17].

Induction of the VZV-specific T-cell immunity, by increasing both the cytotoxic CD8+ lymphocytes, which recognize viral target-proteins and lyse the infected cells, and CD4+ T-lymphocytes, which produce cytokines [8,18]. The VZV-specific T-cell immunity contributes to the limitation of the primary infection and prevents the virus reactivation in neurons as well as the development of a VZV symptomatic disease following exogenous reexposure of the host (memory immunity) [8].

During the lifetime, VZV-specific cell immunity is periodically enhanced by subclinical "endogenous" reactivation of the latent VZV or clinical manifestation of HZ (endogenous boosting). Additionally, "exogenous" exposure to patients with varicella has been shown to induce the boosting of VZV-specific T-cells (exogenous boosting) [16,19].

Induction of the anti-apoptotic protein surviving that inhibits the apoptosis in the epithelial cells of the hair follicles, which correspond to the initial replication sites of VZV in skin [11].

Transmission of VZV

VZV transmission to an immunologically naive person occurs either via droplets and aerosol from oropharyngeal secretions [20] or by direct contact with the infectious virions present in varicella or HZ skin lesions, which remain infectious until they have crusted over [21]. In utero infection can also occur as a result of transplacental passage of virus during maternal varicella infection.

Although VZV is highly contagious, HZ is much less transmittable compared to varicella. Based on studies of transmission among household members, varicella occurs in 15.5% and 71.5% of immunologically susceptible individuals exposed to patients with herpes zoster and varicella, respectively [8,22,23].

Pathophysiology of VZV Infections

Primary VZV Infection – Varicella

Following inoculation into the upper respiratory epithelial or conjunctival mucosa cells, VZV interacts with and infects local immune system cells (dendritic cells and tonsil T- cells) as well as those in adjacent lymphatic tissues [24]. VZV-infected dendritic cells facilitate spread to lymph nodes where resident T-cells become infected [6]. VZV-infected CD4+ cells predominantly show a memory T-cell phenotype and express activation markers and skin homing proteins, such as cutaneous leukocyte antigen (CLA) and chemokine receptor 4 (CCR-4) [8,24]. Primary VZV infection is characterized by the occurrence of cell-associated viraemia, which is followed by the migration of activated

CD4+ lymphocytes to the skin through blood circulation, resulting in the formation of the characteristic varicella vesicular rash. The latter is caused by VZV replication and cytolysis due to cytokine-induced inflammation (IL-1, IL-6, IL-8, IFN- α and TNF- α) [8,15] and the expression of viral lytic proteins [7-8].

VZV latent infection of sensory ganglia

During primary infection, VZV virions gain access to the sensory nerve cell bodies in ganglia by retrograde axonal transport from peripheral skin lesions or via hematogenous spread by T-cell viraemia [6,17] and latent infection is established. Since sensory nerve axons terminate in the dermis, cell-free VZV present at high titers in varicella vesicles have direct access to dorsal root ganglia, cranial nerve ganglia and autonomic nervous system ganglia [25,26].

Given that varicella vesicles may develop on any dermatome, all sensory ganglia can become latently infected and VZV virions are established both in the nerve cell bodies and surrounding satellite glial cells [6,27]. The latent infection is not contagious and is characterized by the presence of the viral DNA (at a frequency of 2 to 9 copies) in 1% to 7% of individual neurons in sensory ganglia, with simultaneous absence of detectable virus replication [4, 25,26].

Reactivation of VZV - Herpes zoster

VZV reactivation occurs when the virus is replicated within the nerve cell bodies and the satellite cells of the sensory ganglia, leading to the formation of intact viral particles. The latter migrate to the skin via anterograde axonal transport causing the HZ vesicular rash in the dermatome that is innervated by the latently infected ganglion, usually without viraemia. The occurrence of HZ in specific dermatomes corresponds to the varicella lesions density [13].

The ability of VZV to induce cell-cell fusion leads to the formation of HZ vesicular skin lesions and the neuron-satellite cell fusion may trigger widespread infection of many additional neurons resulting in extensive eruption [6,13,26].

Herpes zoster is characterized by prodromal pain along one or more skin dermatomes in 70-80% of cases and the appearance of grouped herpetiform vesicles on an erythematous base in segmental arrangement (Figure 1). The vesicular eruption generally occurs unilaterally in the distribution of a sensory nerve. The trigeminal cranial nerve as well as cervical and thoracic sensory nerves are most commonly involved. Many clinical variations are possible and Postherpetic Neuralgia (PHN) is the most common serious complication of HZ [19,27,28].



Figure 1: Characteristic dermatomal distribution of herpes zoster vesicular rash

Virus replication in the sensory ganglia and the subsequent induction of an intense inflammatory response leads to haemorrhagic necrosis and destruction of the nerve cells, as well as fibrosis of the sensory ganglion and nerve [3]. These disorders contribute to the appearance of the characteristic neuralgia of HZ [29] and the absence of the same dermatome involvement in case of HZ recurrence [30].

Although the etiopathogenetic mechanisms triggering the reactivation of latent VZV have not been identified [19] the following hypotheses have been suggested:

Disturbances of host intrinsic cellular mechanisms that might restore viral gene silencing resulting in abortive replication [6], such as the Promyelocytic Leukemia (PML) protein, also known as the nuclear domain 10 (ND-10) protein, a predominant component of nuclear structures that exerts antiviral effects [6,26]. The viral ORF61 protein leads to host ND-10 structures degradation facilitating the virus replication [6,8,26].

Lack of the VZV-specific immune surveillance during latency, and the simultaneous absence of CD8+ T-lymphocytes surrounding the latent VZV-containing neurons [26]. The latter may be related to down-regulation of MHC class I molecules expression by the viral protein ORF66, resulting in inhibition of viral antigens presentation to CD8+ T-lymphocytes [26,31], coupled with the naturally low expression of MHC class I protein in neurons [3,8].

Immunosenescence, which is characterized by the natural decline in T-cell function with advancing age [26], and therefore a reduction of the VZV-specific cellular immunity in otherwise healthy individuals, without affecting the humoral immunity [13,19].

Immunosuppression, even temporarily, induced by transient psychological stress, injury, or surgery [26,32]. Herpes zoster may occur within a period of up to 6 months [19] after the last stressful life event [32]. Mechanical trauma has been found to be highly associated with the development of HZ in the same site [33].

Epidemiology of Herpes Zoster

Incidence and risk factors

More than 95% of immunocompetent individuals above 50 years of age are VZV seropositive, due to primary VZV infection with wild-type VZV or varicella vaccination [19], and are, therefore, at risk of developing HZ [34,35]. Recently, population-based studies have shown increasing rates of HZ associated with:

- population ageing [36,37]
- increased use of immunosuppressive drugs [20,37] and
- population-wide childhood VZV vaccination [37] resulting in less 'exogenous boosting' of VZV-specific cellular immunity [17,35,37]. However, the risk for vaccine Oka strain induced zoster is lower than that following wild-type varicella infection [19].

The annual incidence of HZ in Western countries varies from 3.2 to 4.2 cases per 1,000 person-years (PY). The incidence increases with advancing age and ranges from 7.8 to 10 cases per 1,000 PY in adults aged 60 and 80, respectively [8,19,38]. It has been estimated that the lifetime risk of HZ in the general population is about 20-30%, and rises up to 50% in people aged over 80 [33-34]. Two-thirds of HZ cases occur in individuals aged 50 years or over [38], and only 5% of HZ patients are younger than 15 years [8,34,38].

In addition to increasing age, other risk factors for developing HZ include:

Systemic immunosuppression caused by:

- HIV infection, with incidence rates of 29.4-51.5 cases per 1,000

PY. HZ may occur at any time in the course of HIV-induced immunosuppression and may be the first clinical manifestation of undiagnosed HIV infection, especially, in young people [2,19,39].

- Hematologic malignancies and solid tumors, with incidence rates of 31 and 12 cases per 1,000 PY, respectively [40]. The incidence of HZ is up to 5 times higher in patients with hematologic malignancies and nearly 2-5 times higher in those with solid tumors compared to the general population [40-41]. Approximately 3% of the pediatric zoster cases occur in children with malignancies [42-43]. An increased risk of subsequent cancer after zoster in adults aged 18 to 50 has been reported. For all cancers combined, the hazard ratio is 2.42 and the median time from HZ to cancer diagnosis is over 2 years [44]. Thus, the index of suspicion for underlying immunosuppressive disease should be higher in young people with HZ [33].
- Transplantation of hematopoietic cells and solid organs, with HZ occurrence in a rate of 13-55% and 5-17%, respectively [19].
- Use of immunosuppressive drugs or exposure to radiation [19,45].

Underlying inflammatory diseases, and in particular autoimmune diseases such as SLE, rheumatoid arthritis, Wegener's granulomatosis, ulcerative colitis [17,19].

Chronic diseases, such as asthma, chronic renal disease, depression, multiple sclerosis [19].

The age at the time of primary VZV infection. In cases of varicella infection in utero or in early infancy, wherein the immunity is not fully developed [42,43], the risk for HZ occurrence during childhood is increased more than 35-fold [7,19] compared with the risk for primary VZV infection occurring after infancy [19].

Geographic or seasonal variation, sex, race

Herpes zoster does not exhibit geographic distribution or a seasonal pattern, although an increase of the incidence has been observed during summer months, with UV-exposed skin/anatomic sites being the most susceptible [19]. The HZ rate is higher among women compared to men (male/female ratio around 1.4), with an increased age-specific risk for developing Postherpetic Neuralgia (PHN) [19]. The HZ incidence is lower among coloured [19,38] than in white adults, probably due to true differences in the immune response to VZV, or in lifetime occurrence of varicella [46].

Recurrences

Herpes zoster recurrence is rare, however, it is more common than previously reported [37]. In some cases, it might be due to a different virus strain than the one that caused the primary infection or the initial HZ episode [9]. Approximately 4-6.2% of the immunocompetent patients will experience a recurrent episode, usually within 4-8 years after the first episode [37,40,47]. Recurrence appears to be more common in people with longer-lasting zoster-related pain, which has been shown to be associated with greater severity of the initial HZ rash and higher intensity of pain [47].

Repeated relapses are almost exclusively observed in immunocompromised individuals, such as HIV infected and solid organ transplant patients (in 25% and 9%, respectively) [5], with lung and heart recipients appearing to be at highest risk probably related to the increased intensity of immunosuppression [41].

Given that the exposure to varicella boosts immunity to HZ and might protect against HZ occurrence, a 25%-75% reduction in risk for zoster among persons with one to four reexposures to varicella infected patients compared to those with no exposures has been reported [5,19].

Vaccination

The efficacy of the live attenuated herpes zoster vaccine (ZVL) supports the 'exogenous boosting' hypothesis [48]. It contains the same Oka strain of live attenuated VZV used in the varicella vaccine, but its immunogenic potency is at least 14-times greater [49] than the latter. The HZ vaccine is administered to immunocompetent persons aged ≥ 50 years (according to FDA) [50] or aged ≥ 60 years (according to Advisory Committee on Immunization Practices, ACIP) [51], including those with a previous HZ episode or chronic medical conditions [49].

VZL has been shown to reduce the HZ incidence and postherpetic neuralgia by 51.3% and 66.5%, respectively, in vaccinated individuals via exogenous boosting of VZV-specific immunity [19]. However, the HZ vaccine has a relevant declining efficacy in reducing HZ and PHN incidence and burden of illness 5-8 years post-vaccination [49], especially in persons older than 70 years of age.

A novel non-live, adjuvanted recombinant subunit herpes zoster vaccine, known as HZ/su vaccine, which combines a key surface VZV glycoprotein (E) with a T-cell-boosting adjuvant system (AS01_B), showed excellent efficacy of ~97% and 91% in immunocompetent adults ≥ 50 and ≥ 70 years of age, respectively, in phase III controlled trials. Efficacy was unaffected by advancing age and persisted over 3 years, whereas phase I-II trials showed safety and immunogenicity in severely immunocompromised patients [49,52,53].

In October 2017, the US CDC's Advisory Committee on Immunization Practices recommended the HZ/su vaccine as the preferred vaccine for the prevention of zoster for adults aged 50 and older.

Conclusion

Herpes zoster is the clinical manifestation of the reactivation of latent varicella zoster virus infection. In this paper, we report on the pathophysiological and epidemiological aspects of herpes zoster, especially the genomic and biological properties of Varicella-Zoster Virus (VZV), the immunologic abnormalities and pathophysiology of primary VZV infection, latency and recurrences, as well as epidemiology and immunization. We also mention the live attenuated vaccine derived from the Oka strain of varicella zoster virus that has been shown to be highly effective and has been introduced into the US vaccination programme since 1996.

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