Review

Advances in Epidemiological Studies of Herpes Zoster

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Abstract

Herpes zoster (HZ) is a varicella zoster virus (VZV) that attacks locality of nerves and skin, resulting in formation of clusters of blisters on the skin connected unilateral facial nerve and accompanying apparent nerve pain. Incidence ranges from 3.2 to 4.2 per 1000 populations per year in the United States. Influence factors of HZ include age, infection history with VZV, vaccination history of varicella vaccine, reduced immunocompetence, and other diseases. Current domestic studies on HZ mainly focus on clinical reports of case treatment. This study reviews advances in foreign epidemiological studies of HZ.

Herpes zoster (HZ) is a skin infection caused by reactivation of varicella-zoster virus (VZV), which is latent in sensory ganglia. Typical features of this infection cause herpes along sensory nerves in corresponding segments and accompanying severe neuropathic pain, seriously affecting quality of life. Several countries, such as the United States, Britain, and Australia, studied epidemiological characteristics of HZ. Current domestic studies on HZ mainly focus on clinical reports of case treatment. Epidemiological studies on HZ are few, and they cannot provide basis for formulating strategies regarding HZ immunity. This study introduces advances in foreign epidemiological studies of HZ.

Pathogenesis and infection of HZ

VZV belongs to herpes virus subfamily. Clinical manifestation of initial infection is varicella, and susceptible age is those of children. VZV is transmitted to epithelial tissues after mass propagation and infects junction cells between dermis and epidermis, leading to characteristic blister damage. Simultaneously, the end of sensory axon is located at the junction between the dermis and epidermis at the bottom of skin blisters. After recovery from blisters, VZV proceeds to axons and becomes latent in nerve cells of

sensory ganglia. Latency and reactivation of VZV are closely related to specific immunity. After initial infection with VZV, the body produces specific immunities against VZV; these immune reactions include VZV-specific antibodies and T cell-mediated immunity, which play important roles in maintenance of VZV latency and HZ prevention. When immune level decreases, VZV is activated, and HZ infection occurs.

HZ patients afflicted with rash to incrustation are infectious^[1-3]. Breakage of HZ contains high concentrations of VZV, which can form aerosols and spread^[4]. Susceptible population can be infected and acquire varicella. HZ is less infectious than varicella because of differences in their transmission routes. A study showed that in the same family, varicella was acquired by 15.5% of persons in contact with HZ patients and 71.5% of individuals in contact with varicella patients^[5]. Therefore, HZ patients should be isolated until herpes scab. Close contacts should undergo medical observation, and varicella susceptible population should be inoculated with varicella vaccine to prevent development of related diseases.

Epidemiology of HZ

Incidence level

No country in the world classified HZ as notifiable infectious disease. Some countries conducted studies on incidence level of HZ. In the United States, incidence ranges from 3.2 to 4.2 per 1000 populations per year. With increase in age, incidence of HZ increases, and incidence rate of people over 60 reaches 10 per 1000 populations per year^[6–8]. HZ also exhibits recurrence. A Minnesota study followed up for six years showed that recurrence rate of HZ reaches 14 per 1000 populations per year^[9]. Studies in the US and UK indicated that hospitalization rate of HZ totals 2.1–16.1 per 1,000,000 populations per year^[10, 11]. Hospitalization rate of HZ increases with age. A US study showed that hospitalization rate of HZ among people aged at and over 85 years old was 75 times higher than that of people under 30^[12]. A study in Australia showed 1% mortality rate in hospitalized patients primarily diagnosed with HZ. Mortality rate of patients over 65 years old is 10 times higher than that of younger people^[13]. Immunosuppression is one of the major risk factors leading to hospitalization and death in patients with HZ. Up to 30% of hospitalized patients with HZ and 52% of deaths are accompanied by one or more immune system damages, such as malignant tumor, leukemia, and HIV infection.

Risk factors

Age Age is the most important risk factor of HZ. Studies of different designs and in different areas all showed that incidence of HZ increases with age. Incidence of children under 10 reaches 0.74 per 1000 populations per year. Incidence increases gradually in the ten-year-old age group. From 50–60 years old, this increase becomes significant; HZ incidence in people aged 80 to 90 totals 10 per 1000 populations per year^[14]. Specific immune level of organism decreases with age. After initial infection of varicella, antibody levels decrease with time; this phenomenon may be due to increased incidence of HZ with age^[15]. Age is also the main risk factor for neuralgia in patients with HZ. A number of studies showed that risk of HZ accompanied by neuropathic pain increases with age, especially for people over the age of 50; among these individuals, 80%–85% experience neuralgia^[16]. Risk for at least two months of neuropathic pain is 27.4 times of that of population under 50^[17].

Gender No agreed conclusion can explain the relationship between gender and incidence of HZ. In a prospective cohort study in New Zealand, risk of HZ in women was 38% higher

than that in men after adjustment for age and other risk factors (95% confidence interval was 1.22–1.56)^[18]. Other studies also indicated that incidence of HZ in women was higher after standardization of age^[19]. However, parts of studies did not show statistical differences in incidence of HZ between genders^[20, 21].

Seasonal and geographical factors Most studies did not found seasonal incidence of HZ^[22]. Several studies showed high incidence during summer, when ultraviolet rays possibly stimulated HZ in exposed skin^[23, 24]. No studies showed that incidence of HZ is related to regional latitude and distribution of rural areas^[25].

VZV infection history Reactivation of latent VZV causes HZ. Therefore, previous VZV infection serves as necessary condition for occurrence of HZ^[26]. Serum antibody levels showed that 99.5% of people over 40 were previously infected by VZV. Though most people did not remember suffering from varicella, VZV infection rate reminded elders of risk of HZ^[27].

VZV contact history Individuals exposed to varicella can reduce risk of HZ by increasing levels of VZV-specific antibodies. British monitoring data analysis showed that incidence of varicella among children under five was inversely proportional to that in adults aged 15–44 years old^[28]. Multivariate analysis showed that compared with those who were not exposed to varicella, exposure to varicella for three to four times decreases risk of HZ by 74% times, and exposure of less than three times also reduces such incidence^[29]. A cohort study of UK sentinel surveillance showed that incidence of varicella increased in adults with access to varicella and living with children, whereas incidence of HZ decreased by 25%. This protection can last for 20 years (95% confidence interval was 7–14 years)^[30]. Other evidence support the opposite view that exposure to varicella does not reduce risk of HZ. Women may be more exposed to children with varicella, whereas studies showed much higher risk of HZ in women than in men.

History of varicella vaccine immunization In varicella vaccine inoculator, attenuated vaccine strains can lead to VZV recessive infection, virus reactivation, and HZ infection^[31]. In clinical manifestations, distinguishing HZ caused by vaccine strain and wild strain is not possible. Varicella

vaccine inoculator may already be infected with the virus or was infected with the virus due to immune failure after vaccination. Therefore, estimating risk of HZ caused by vaccine strains is improbable. Compared with individuals who were previously infected with varicella, risk of HZ reduces by 65% in immunodeficient children with history of one dose of varicella vaccine, and risk of HZ also reduces in children with normal immune function [32].

Reduced immunocompetence Unlike other infectious diseases that can be prevented by vaccines, direct cause of HZ infection is not exposure to pathogens. However, latent VZV is activated after specific biological changes. Immune dysfunction is a risk factor for HZ and severe complications. Incidence of HZ in patients with malignant tumors reaches approximately 5%, which is higher than that of normal population of the same age [33]. Risk of the disease is determined by nature of tumor and treatment [34]. Incidence of HZ of patient He Jinjie reached as high as 27.3% [35]. After hematopoietic stem cell transplantation, HZ becomes much common; incidence rate totals 13%–55% in the first year after operation [36]. After organ transplantation, incidence of HZ reaches 5%–17%; the majority of HZ occurs one year after operation [37]. Incidence of HZ in HIV-infected adults totals 29.4–51.5 per 1000 populations per year; this value is 12–17 times higher than that of HIV-negative patients [38–40]. Incidence of HZ in HIV-infected children is much higher compared with HIV-negative children; in children at inhibitory stage, incidence reaches 467 per 1000 populations per year [41].

Other diseases Risk of HZ increases in patients with inflammatory diseases. Morbidity of HZ in patients with systemic lupus erythematosus reaches 15–91 per 1000 populations per year [42, 43]. Incidence of HZ in patients with arthritis is approximately 10 per 1000 populations per year [44]. Morbidity of HZ in patients with Wegner's granulomatosis totals 45 per 1000 populations per year [45]. Crohn's disease and ulcerative colitis are both related to incidence of HZ, and risks amount to 1.6 and 1.2, respectively [46]. Risk of HZ in patients with inflammatory disease also increases. Two studies showed association of diabetes with HZ [47]. However, other studies failed to verify their correlation [48]. One study reported an increased risk of HZ in patients with multiple sclerosis [49].

Other risk factors Trauma or surgery can activate latent VZV in the dorsal ganglion, thus increasing risk of HZ [50–52]. A case–control study showed that incidence of such case is close to that in the control group without herpes skin trauma. However, in patients with HZ, the proportion of trauma within a few months before onset of skin lesions was significantly higher than that in the control group; risk reached 12.1 (95% confidence interval was 1.5–97.6) [53]. Psychological stress plays a certain role in HZ pathogenesis. A case–control study showed that incidence of HZ was associated with stress in life within six months [54]. Mechanisms of these risk factors causing incidence of HZ require further elucidation. However, immunity factors play important roles in HZ occurrence. Genetic predisposition of HZ was also reported. Polymorphism of interleukin-10 gene is related to HZ pathogenesis [55, 56].

HZ, especially post herpetic neuralgia, seriously affects patients' body, psychology, daily life, and work. Onset risk is associated with age, VZV infection history, reduced immunocompetence, and other diseases. HZ vaccine was listed abroad in 2006 and was recommended for use in elderly over 60 after estimation of HZ burden in the United States. Formulation of vaccine immunization strategies in different countries depends on epidemiological characteristics of national diseases, efficacy and safety of vaccine, and economic burdens. Few studies focused on pathogenesis, disease burden, and risk factors of HZ in China. Thus, basic data are insufficient when HZ vaccine becomes listed in our country in the future. In this sense, providing reliable evidence for development of HZ vaccine strategies poses a challenge. Therefore, our country should investigate or establish a HZ monitoring system, understand epidemiological characteristics and risk factors of HZ, provide scientific basis for prevention and control of herpes zoster, and conduct public health strategies for vaccine use.

Declarations

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No.

Competing interests

The author declares that he has no competing interest.

Authors' contributions

Y Liu made the literature analysis and wrote, discussed and revised the manuscript of this review.

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