DOI:10.5958/j.2319-5886.2.4.154

International Journal of Medical Research & Health Sciences

www.ijmrhs.com Volume 2 Issue 4 Oct - Dec Coden: IJMRHS Copyright @2013 ISSN: 2319-5886

Received: 10th July 2013 Revised: 8th Aug 2013 Accepted: 15th Aug 2013

Review article

HERPES –ZOSTER: AN UPDATE

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ABSTRACT

Herpes zoster (HZ) is the reactivated form of the Varicella zoster virus (VZV), the same virus responsible for chickenpox. The condition produces a striking picture, with a blistering, crusting rash confined to well demarcated areas of the body. Latency is typically life long, and Herpes Zoster is caused by viral reactivation from the latent state. The survival of Varicella Zoster Virus in human for several million years attests to its success. Present review provides an overview of the natural history, epidemiology and possible complications of varicella zoster virus along with diagnosis, prophylaxis and different treatment modalities.

Keywords: Varicella, Herpes, Shingles

INTRODUCTION

The term herpes comes from the ancient Greek word meaning to *"creep or crawl"*. The human herpes family is officially known as *Herpetoviridae***.**[1] Eight different types of herpes viruses are known whose primary hosts are humans. They have been officially designated 'Human herpes types 1-8.[2] Human herpes simplex viruses type 1 and type 2, both, are cytolytic in nature and have neurons as the site of latent infection, whereas human herpes viruses type 4 (Epstein barr virus), type 6 and type 7 have lymphoproliferative effect. The only known human herpes virus which is cytomegalic is type 5, commonly known as a Cytomegalo virus (**Table 1**). [2,3] In 1889, Von Bokay suggested that varicella (chickenpox) and herpes zoster (HZ) are different manifestations of same virus infection. [2] Varicella Zoster Virus, a neurotropic human herpes virus causes chicken pox and then remains latent for decades in cranial nerve, dorsal root and autonomic nervous system ganglia. The virus gets reactivated after a variable period of time usually ranging from 5-40 years in 15% patients and causes herpes zoster.[4]

Herpes Zoster is more commonly known as shingles, from the Latin *cingulum, for "girdle"*. This is because a common presentation of HZ involves a unilateral rash that can wrap around the waist or torso like a girdle. Similarly, the name zoster is derived from classical Greek, referring to a belt-like binding (known as a zoster) used by warriors to secure armor.[3]

Table.1: **Classification, cytopathology, site of latent infection and common associated diseases of human herpes virus.**[2,3]

Species	Cytopathology	Site of latent infection	Common associated diseases
Herpes simplex virus-Type I	Cytolytic	Neurons	Oral herpes lesions
Herpes simplex virus-Type 2	Cytolytic	Neurons	Genital herpes lesions
Herpes virus- Type 3 Varicella zoster virus	Cytolytic	Neurons	Chickenpox, shingles
Herpes virus- Type 4 Epstein- barr virus	Lymphoproliferative	Lymphoid tissues	Infectious mononucleosis
Herpes simplex virus-Type 5 Cytomegalo virus	Cytomegalic	Secretory glands, kidneys etc	CMV mononucleosis
Herpes simplex virus-Type 6	Lymphoproliferative	Lymphoid tissues	Roseola, mononucleosis syndromes
Herpes simplex virus-Type 7	Lymphoproliferative	Lymphoid tissues	Currently, no human disease definitely linked
Herpes simplex virus-Type 8	-	-	Suspected association with Kaposi's sarcoma

STRUCTURE

Varicella zoster virus belongs taxonomically to the group of alpha herpes viruses. It has double-stranded, linear DNA, consisting of about 125-kilobase pairs, encased within an icosahedral protein capsid, composed of 162 capsomers. The nucleocapsid is surrounded by a pleomorphous outer shell (tegument with envelope membrane), which is rich in phosphoprotein. Diameters vary between 150 and 180 nm due to the variability of the outer shell.[5]

EPIDEMIOLOGY

A systemic review published in 2004 found the overall incidence of zoster among immunocompetent subjects ranged from 1.2-4.8 per 1000 people; recent studies from United Studies and France have also reported disease incidences within this range.[6] The estimated annual incidence of HZ in Cebrián-Cuenca et al. (2010) study was 4.1 per 1,000 persons >14 years of age.[7] The increased risk of zoster among older individuals may be due to waning of specific immunity with increasing time since primary infection (varicella), or may occur as part of the generalized decay in cell-mediated immunity that occurs with age (immunosenescence), an important factor in the increased susceptibility to infections, malignancies, and autoimmune disorders in the elderly. Little is known about the determinants of either generalised or VZV-specific immune decay.[8]

CLINICAL MANIFESTATIONS

The prodromal syndrome stage presents as sensations described as burning, tingling, itching, boring, prickly or knife-like occurring in the skin over the affected nerve distribution.[9] Pain is the most annoying symptom of herpes zoster. It often precedes and generally accompanies the rash.[10] Zoster rash is a vesicular eruption on an erythematous base in one to three dermatomes, usually accompanied by severe, sharp, lancinating, radicular pain, itching, and unpleasant, abnormal sensations (dysesthesias). Patients may also have decreased sensation in the

affected area, while the skin is exquisitely sensitive to touch (allodynia).[11]

Within 3 to 5 days of the initial symptoms, an erythematous maculopapular rash erupts unilaterally in the nerves of sensory dermatomes adjacent to the involved ganglia. Over the next 7 to 10 days, the rash progresses to pustules and ulceration, with crusts, scabbing, or both, this can persist for up to 30 days in the acute phase. At the end of the healing process, altered (post inflammatory) pigmentation may develop along the affected dermatome. [12] Complete healing may take more than 4 weeks.[13] The cutaneous eruption is unilateral and does not cross the midline. Simultaneous involvement of multiple noncontiguous dermatomes virtually never occurs in immunocompetent patients, although lesions overlap adjacent dermatomes in 20 percent of cases.[14]

DIAGNOSIS

***Differential diagnosis*:** Definitive diagnosis involves a process of elimination, with several likely aetiologies in the differential diagnosis. A differential diagnosis should include trigeminal neuralgia, maxillary sinusitis, periodic migraines' neuralgia, myocardial pain, atypical facial pain and Munchausen's syndrome.[9]

Laboratory diagnosis: Histopathological features; cytologic alterations are virtually identical to those of human herpes simplex virus. Intranuclear inclusions- lipschutz bodies may be seen in smears prepared by scraping of the base of the early vesicles (Tzanck smears) and stained with toulidiene blue, Giemsa or PAP. Infected cells exhibit acantholysis, nuclear clearing and nuclear enlargement that is ballooning degeneration. Connective tissue shows inflammatory cells infiltate.[1,2]

On the basis of histological features one can't rule out the definite diagnosis of herpes zoster infection form herpes simplex. Co-relation with clinical features is required. **Table 2** enumerates some differences between herpes zoster and recurrent herpes simplex infection.

Table 2: **Difference between herpes zoster and recurrent herpes simplex[15]**

Characteristic	Herpes Zoster	Recurrent Herpes Simplex
Sites of latent infections	Sensory neurons in all sensory ganglia	Sensory neurons in trigeminal and sacral sensory ganglia
Viral gene expression during latency	Several "immediate early" and "early" VZV proteins are synthesized	No HSV proteins are synthesized; only "latency-associated transcripts"
Symptomatic reactivation of latent virus	Infrequent (rarely involves the same dermatome)	Frequent (usually involves the same dermatome)
Asymptomatic reactivation with asymptomatic virus shedding	None	Frequent
Proportion of the affected dermatome involved by rash	Large (sensory fields of many neurons)	Small (often the sensory field of a single neuron)
Consequences of reactivation of latent virus	Extensive ganglionic pathology and neuronal death	No obvious ganglionic pathology or neuronal death
Postherpetic neuralgia	Common	Extremely rare
Frequency of symptomatic reactivation	Increases with increasing age (and time after primary infection)	Decreases over time after primary infection

In most cases, a diagnosis of VZV infection is based on the characteristic prodrome of symptoms and the pattern of skin eruptions. Virus isolation can be attempted from the buccal or cutaneous lesion in the early stages by inoculating human amnion, human fibroblasts, HeLa or Vero cells but typically viral culture test.[2] Viral culture, antigen detection test by using modified Tzank technique. Serological test via ELISA or latex agglutination, polymerase chain reaction (PCR) is useful to detect VZV DNA.[16]

COMPLICATIONS

***Postherpetic Neuralgia (PHN)*:** Postherpetic neuralgia (defined as pain that persists more than 30 days after the onset of rash or after cutaneous healing) is the most feared complication in immunocompetent patients.[14] Clinically significant PHN was described by R. Edgar Hope-Simpson in 1975 as a chronic neuropathic pain syndrome that may contribute recovery from an acute attack of herpes zoster.[17] Although it has a high morbidity, the mechanism causing PHN remains unknown, its occurrence cannot be predicted at the time of zoster and its treatment is still highly unsatisfactory and generally ineffective.[18]

***Cutaneous complications*:** Cutaneous dissemination of herpes zoster defined as more than 20 vesicles outside the area of primary or adjacent dermatomes and occurs in approximately 10% of immunocompromised persons.[10] Acute and chronic complications involving the skin are frequent. The skin is predominantly affected by bacterial secondary infections in the acute stage. Ecthymiform ulcerations may develop. Other cutaneous complications include: hemorrhages (zoster hemorrhagicus), purulent gangrene (zoster gangrenosus), and persistence of lesions and dissemination (zoster disseminatus) in immunocompromised patients. A manifestation of psoriasis vulgaris (Kobner's phenomenon) may occur with chronic hypo-pigmented and depigmented scar formation.[19]

Herpes zoster ophthalmicus (HZO): Herpes zoster ophthalmicus occurs when reactivation of the latent virus in the trigeminal ganglia involves the ophthalmic division of the nerve.[20] While HZO does not necessarily affect the structures of the eye, many of the acute and long-term complications associated with the disease are the result of direct viral toxicity to the eye or the ensuing inflammatory response within the eye.[21] Hutchinson's sign is defined as skin lesions at the tip, side, or root of the nose and is a strong predictor of ocular inflammation and corneal denervation in HZO, especially if both branches of the nasociliary nerve are involved.[22]

Ramsay Hunt syndrome and other neurological syndromes: Less common manifestations of zoster include the Ramsay Hunt syndrome (involvement of the geniculate ganglion of the facial nerve) which manifests as vesicles in the external auditory canal and palate associated with loss of taste to the anterior two-thirds of the tongue and facial weakness.[23]

Neurologic symptoms (headache, fever, vomiting, and altered sensorium) most often occur about 1 week after the onset of the varicella rash. The onset of symptoms may be abrupt or gradual and is accompanied by seizures in 29%–52% of cases.[24]

Prophylaxis

The live attenuated Oka vaccine was developed in 1974 by Takahashi in Japan. Virus from a child with varicella was serially passaged at low temperature (34°C) in human fibroblasts, followed by a passage in guinea pig embryo fibroblasts and the production of a standardized seed lot in human diploid cells. Production of the vaccine is now standardized according to the World Health Organizations' "good manufacturing process".[25]

Recommended dose for children 1-12 yrs is a single subcutaneous dose, while in case of adults and adolescents 2 doses (6-10weeks apart) should be given.[2]

TREATMENT

The objectives of treating HZ are to control acute pain, accelerate rash healing, minimize systemic complications and reduce the risk of PHN and other complications.[26] In most cases, HZ is self-limiting and treatment with analgesics suffices. Based on level I evidence, antiviral medication might have some effect on the severity of acute pain and the duration of skin lesions.[27] Most commonly used drugs used in treatment of herpes infections are given in **Table 3**.

Table 3: **Treatment of Acute Herpes Zoster**.[13]

Class of agent and usual dose	**Patients in whom treatment is indicated**	**Comments**
Antivirals *Famciclovir: 250 mg orally 3 times daily for 7 days. *Valacyclovir: 1 g orally 3 times daily for 7 days. *Acyclovir: 800 mg orally 5 times daily for 7 days. *In immunocompromized patients/disseminated disease: acyclovir, 10 mg/kg intravenously every 8 h until resolution of cutaneous / visceral disease	*All who present within 72 h of rash onset. *Consider antivirals in those who present >72 hrs after rash onset if they have the following characteristics: - Age >50 y - Immunocompromised status - Severe pain at presentation -High-risk lesions (involving tip of nose/eye)	Antivirals reduce both acute symptoms and subsequent risk of PHN.
Glucocorticoids Prednisone: 60 mg orally for 7 d, then taper for next 2 weeks.	Those who are older and/or those with severe pain as long as no contraindications exist.	Corticosteroids have no effect on the subsequent development of PHN and should be used with antivirals, never alone; significant adverse effects are possible.
*Pain medications *Tramadol *Oxycodone/acetaminophen	Most will require some type of pain medication.	Opioids should be used with caution in elderly patients. Prophylactic laxatives and stool softeners should be considered when prescribing opioids.

CONCLUSION

Herpes zoster represents a mode of evolutionary adaptation by the VZV which is an obligate human parasite. Normal aging, poor nutrition, and immunocompromised status correlate with outbreaks of herpes zoster, and certain factors such as physical or emotional stress and fatigue may precipitate an episode. In small countries, the susceptibilities are completely eliminated by varicella infection in childhood. Therefore, the ability of the virus to remain latent and reappear as zoster years later confers on it a great survival advantage.

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