An Insight to Herpes Zoster Review Article

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Abstract- Herpes zoster (or simply zoster) is an acute, self-limiting viral infection characterized by painful vesicular eruptions with erythema typically present as unilateral dermatomal rash. It is caused by reactivation of dormant varicella zoster virus. About 1 million patients per year are affected by this condition. It mainly affects the elderly and persons with waning cell mediated immunity. If left untreated it may lead to various complications of significant morbidity leaving a considerable effect on quality of life as well as economic status of the patient; the most serious complication being the post herpetic neuralgia, a chronic neuropathic pain syndrome which leaves the patient in a debilitating state. This review article provides an overview of the disease and emphasizes more on the classical features and conventional treatment modalities of zoster thus enabling the oral physician to make early diagnosis and give prompt treatment, which is the mainstay for the management of the disease.

Keywords: herpes zoster, shingles, zona, varicella zoster virus, zoster sine herpete, post herpetic neuralgia, dermatomal rash, vaccine.

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I. INTRODUCTION

Herpes zoster also called zona or shingles is a common viral disease among the elderly and immunocompromised, is unilateral and associated with painful vesicular dermatomal skin rash and vesicles, frequently in a striped pattern.1

Reactivation of varicella zoster virus (VZV) causes herpes zoster (HZ).2 HZ is derived from Greek word herpein meaning to creep or spread; zoster meaning girdle or zone, hence the name zona (warrior armour binding in a belt-like fashion).2,3 Shingles, derived from Latin cingulum meaning girdle (unilateral rash that enfolds like a girdle around the torso).3

II. ETIOPATHOGENESIS

HZ, with a lifetime risk of 10-30%, affecting about 1 million patients per year is caused by VZV.1,4 VZV belongs to alpha herpes virinae and consists of an icosahedral nucleocapsid enclosed in lipid envelope with double stranded DNA at its centre.2,3 The molecular weight and diameter is approximately 80 million and 150-200 nm respectively.2

HZ, a highly transmissible disease may spread either by respiratory droplets or direct contact.6 VZV first enters the host and causes infection of respiratory tract or epithelium of the conjunctiva.6 It then replicates and multiplies; and then penetrates the reticulo-endothelial system from where the blood and lymphatics carry it throughout the body.2,6 It then travels via mononuclear cells and spreads to epidermis via capillary epithelium where VZV destroys basal cells.6 This leads to generalized rash of chickenpox. After the fall of the initial outbreak, VZV retreats into perineural satellite cells of dorsal nerve root ganglion where it remains inactive for years.2,6 Reactivation of VZV by any triggering factor causes an outbreak and the secondary infection of HZ.2 Therefore, the primary infection by VZV causes chickenpox (varicella) in children whereas shingles is caused by recurrent secondary infection in adults.5 Incubation period for varicella ranges from 14-16 days; chances of transmission being high between 10-21 days after initial exposure.2 Transmission cannot occur after crust have dried. Indirect transmission does not occur.2 Most commonly affected dermatomes are thoracic (45%), cervical (23%) & trigeminal (15%).7 HZ may affect sensory ganglia & its cutaneous nerves (Strommen et al. 1988).8 Thoracic and lumbar dermatomes are involved more commonly as compared to craniofacial area.8 The virus may remain latent for decades together in the cranial nerve, dorsal root and autonomous nervous system ganglia along the entire neural axis.8 2 main mechanisms have been developed by VZV to escape the human immune system:3

a. Initially, VZV remains inactive in sensory ganglion, thereby restricting the expression of viral proteins. At this stage virus does not replicate but retains its capability to revert to pathogenic nature at anytime.3

b. Down regulating the expression of antigens of MHC Class 1 on the surface of infected cells, leads to decrease in surface expression of its proteins, thereby restricting the presentation of viral peptides to cytotoxic T-cells which ultimately leads to escape of lysis by virus infected cells.3

Most critical complication is a form of neuropathy of pain called post herpetic neuralgia (PHN).9

The pathophysiology involved is injury affecting the neurons of both central and peripheral nervous system generates spontaneous discharges.4 It also decreases the action potential threshold which in turn decreases the generation of disproportionate pain, even with non-specific stimuli.4

III. EPIDEMIOLOGY & PREDISPOSING FACTORS

HZ, a common disease with a lifetime risk of 10-30% which increases to 50% among individuals ≥85 years.1 In Australia by the age of 30 years more than 97% of population have antibodies to VZV, which
confirms that they have been already infected with virus. Thus, the entire adult population is at a high risk of HZ.\(^5\) 1.2-4.8 per 1000 people per year is the total incidence among immunocompetent persons.\(^1\) HZ ranges from 14.5-53.6 per 1000 persons-years in immuno-suppressed patients.\(^1\) HZ increases with age with approximately 14.2 per 1000 people per year in persons ≥50 years in USA, UK, Italy and Germany.\(^1\) Recurrence is seen in approximately 4% of patients who develop HZ.\(^10\) HIV patients are 10 times more prone to develop HZ compared to general population.\(^1\) HZ in organ transplant patients ranges from approximately 22-per 1000 person-years overall, with increased predilection among African-American patients (37.6 per 1000 persons-years) and heart transplant patients (40 per 1000 person-years).\(^1\) HZ incidence is increased in patients treated with monoclonal antibody-TNF inhibitors and various biologics (19.1 per 1000-person-years) compared to non-systemic therapy patients (4.6 per 1000 person-years).\(^1\) HZ is more liable in individuals who suffer with leukemia, lymphoma, metastatic malignancy, autoimmune disorders like SLE, RA, Wegener’s Granulomatosis, Diabetes, COPD, Patients on cytotoxic drugs or steroids & those receiving chemotherapy.\(^1\) Psychological stress may also contribute to HZ.\(^3\) Female predilection for HZ (Thomas and Hall’s systematic review).\(^1\) Malnourishment leads to decrease in cell-mediated immunity thus increases susceptibility to HZ. Alcohol and smoking affect on HZ is still unclear.\(^1\) Climatic changes also influences shingles wherein persons residing in temperate climate and northern latitude are at an increased rate of developing shingles.\(^3\) Another risk factor to HZ is mechanical trauma and immunotoxin exposure.\(^1\) Prior infection with VZV (chickenpox, vaccine) is an important predisposing factor for the development of HZ.\(^5\) Association between varicella & HZ was first made in 1892.\(^11\)

### IV. Clinical Features

HZ presents as an acute, sporadic, self-limiting, painful unilateral vesicular dermatomal rash, often lasts for approximately 10-15 days.\(^5\) Pain and rash are the cardinal features of HZ.\(^12\) The prodromal (pre-eruptive) stage is characterized by pain which may be intermittent/continuous, boring, tingling, itching, burning, prickling or knife-like in the epithelium surface supplied by the affected sensory nerve.\(^3,13\) This severe neuralgia is caused due to viral replication which in turn leads to active ganglionitis with resultant neuronal necrosis.\(^13\) Prodrome may also be associated with mild fever, headache, malaise, dysesthesia.\(^3\) The cutaneous features are preceded by prodromal stage (continue for 3-5 days) in 80% patients (Strommen et al. 1988, Carmichael 1991, Millar & Troulis 1994).\(^3,6\) Odontalgia may be the only oral manifestation present at this stage (Barrett et al. 1993, Law & Lilly 1995).\(^6\)

The Acute (active) phase is characterised by unilateral dermatomal rash associated with malaise, headache, mild fever and nausea. Rash appears proximally and spreads distally.\(^3\) The rash advances in 12-24 hours from erythematous papules and oedema to vesicles and finally within 1-7 days it advances to form pustules.\(^6\) The pustules then dry and form painful crust which within 14-21 days fall-off, therefore leading to formation of macular and erythematous lesions which usually heals to form hypo/hyper pigmented scars.\(^6\) In severe cases, hemorrhagic necrosis may lead to loss of areas of epidermis and dermis (Strommen et al. 1988, Carmichael 1991).\(^6\) Intraoral lesions usually appear after cutaneous rash.\(^3\) HZ without rash, condition termed as Zoster sine herpete, is seen in rare cases wherein the affected patients suffer with pain which is sudden, severe and hyperesthesia over a specific dermatome.\(^13\) Chronic neuropathic pain syndrome stage is also called as Post Herpetic Neuralgia (PHN).\(^6\) Dworkin defined PHN as “a significant pain or abnormal sensation 120 days or more after the presence of initial rash.”\(^14\) It occurs in 20% of the affected patients.\(^4\) PHN can be described as pain comprising of 3 prominent components:\(^6\)

I. Constant, usually deep pain
II. Brief, recurrent shooting pain
III. Alloodynia - sharp, radiating dysesthetic sensation caused by even slight touching (Rowbotham & Fields 1989).

### V. Oral Manifestations

Oral complications are seen when HZ affects the Trigeminal Nerve (18-20% cases).\(^11\) Unilateral multiple vesicular eruptions (1-4 mm) with erythema is seen intra orally.\(^11,13\) Vesicles on palate, uvula, tonsils, tongue, buccal mucosa and floor of the mouth are seen depending upon the branch involved.\(^11\) Apart from odontalgia, devitalised teeth, internal resorption, pulpal necrosis, developmental anomalies, sudden exfoliation of teeth, facial scarring, jaw osteonecrosis, severe periodontitis may also be appreciated.\(^11\)

### VI. Complications

a) Acute complications

May affect brain (Meningoencephalitis, Asptic meningitis, Cranial & Peripheral nerve palsies); Ocular complications (Conjunctivitis, Episcleritis, Uveitis, Keratitis, Secondary Glaucoma, loss of Corneal Sensation, Optic neuropathy, Pitosis, Mydriasis); lungs (Neural Bronchitis, Pleuritis, Pneumonia); kidneys (Acute Renal necrosis); GIT (gastritis/ Enterocolitis); CVS (Pericarditis, Myocarditis); liver (hepatitis); Miscellaneous (Esophagitis, Arthritis, Septicemia, Cutaneous VZ dissemination, Bacterial Superinfection, Zoster granulosum, Zoster hemorrhagicus).
b) **Chronic Complications**

PHN; dermatologic complications (Scal formation, Hypopigmentation); Ocular complications (Chorio-retinitis, Atrophy of optic nerve, Progressive Outer Retinal Necrosis); Deafness, Autonomic dysfunction, Bladder dysfunction; Granulomatous cerebral angiitis, Diaphragmatic paralysis, Guillain-Barre syndrome. Hutchinson’s sign (unilateral cutaneous Zoster lesions of nose tip) is pathognomonic of ocular inflammation and corneal denervation. Argyll-Robertson pupil signifies involvement of ciliary ganglia. Ramsay Hunt Syndrome (triad of HZ of external ear, auditory symptoms, ipsilateral facial paralysis) signifies involvement of geniculate ganglion.

**VII. Investigations and Diagnosis**

Pain, Unilateral nature and Segmental distribution accounts for clinical diagnosis of HZ. Laboratory tests include Tzanck Smear, Viral culture (30-70% sensitive; 100% specific), FNAC from fresh vesicles. Molecular techniques such as Dot-Blot hybridization and Polymerase Chain Reaction for detection of VZV DNA (approximately 100% sensitive). Direct Immunofluorescence assay is a good diagnostic aid.

**VIII. Differential Diagnosis**

Differential Diagnosis may include Trigeminal neuralgia, Maxillary sinusitis, Periodic Migranous neuralgia, Myocardial pain, Atypical facial pain, Munchausen’s Syndrome (Drinnan 1987). The Prodromal stage pain can be misdiagnosed as Pleurisy, Thrombophlebitis, Cardiac disease, Duodenal ulcer, Cholecystitis, Bell’s Palsy, Otitis media, Herniated nucleus pulposus, Sensitive teeth.

**IX. Management**

The primary management comprises of early diagnosis and prompt treatment in the prodromal stage. Management is emphasized towards pain control along with prevention of PHN, supportive care and hydration and definite treatment to decrease the dissemination risk especially in immunosuppressed patients. Patient may be isolated to avoid cross-infection and complete bed rest may be advised. Hospitalization is advised for immunocompromised patients.

**X. Treatment for Herpes Zoster**

Antiviral drugs have been proven to decrease the pain and duration of rash, as well as speed up healing and prevent further complications. Care should be taken to administer antivirals within 72 hours after onset of rash.  

- **Acyclovir**: 800 mg orally five times daily for 7-10 days, or 10 mg/kg IV every 8 hours for 7-10 days
- **Famciclovir**: 500 mg orally 3 times daily for 7 days
- **Valacyclovir**: 1000mg orally 3 times daily for 7 days
- **Brivudin**: 125 mg/day orally for 7 days.

**Recent advanced medications:**

- ASP 2151 Helicase primase inhibitor
- CMX 001 Hexadeoxyxpropyl-cidofovir
- FV 100 two bicyclic nucleoside analogue (BCNA)
- Valamaciclovir Nucleoside analogue (H2G)

Prednisolone (60 mg daily initially, care should be taken to taper the dose for 21 days) may be useful in reducing acute pain. Some cases have been treated with Amtriptilin 25 mg/day for 3 months to prevent PHN. Relief from severe acute pain by administering single epidural injection of corticosteroids (80 mg methylprednisolone) and Local anesthetic (10 mg bupivacaine) may be effective. Opioids and NSAID’s has been proven to be effective to relieve acute pain. Oxycodone decreases acute pain and tramadol prevents PHN.

**XI. Treatment for Post Herpetic Neuralgia**

The main objective of PHN treatment is to relieve pain and require a diverse approach. Multiple medications may be needed.

The first line of treatment for PHN comprises of anticonvulsants like Phenytoin / Carbamazepine / Gabapentin (100-300 mg/day orally at bedtime). Dosage may be increased until therapy is effective and response appreciated but one should be cautious and should keep a constant check on the blood drug level. Topical application of 80% capsacin cream (3-5 times daily) and 5 % lidocaine patch (every 4-12 hours) and Aspirin cream.

The second line of treatment is with opioid analgesics and tricyclic antidepressants like Amtriptylin / Desipramine / Imapramine / Nortryptilin (25 mg/day orally at bedtime). Dosage can be increased until sufficient response is met but maximum dosage should not exceed 150 mg/day.

Systemic Corticosteroids to prevent PHN is controversial. Combination of intralesional steroids and Local anesthetic’s have been proposed to hasten healing and prevent PHN.

Selective Serotonin Norepinephrine Reuptake Inhibitors (SSRI’s) may be administered in patients who cannot tolerate TCA’s.

**Newer advances:**

- Electrical Stimulation of Thalamus
- Anterolateral Cordotomy
- Intercostal Nerve Cryotherapy
- Pulsed Radiofrequency Ablation
- Spinal cord stimulation
- Botulinum toxin injection
Various natural therapeutics may include multiple nutrients (vitamin A, B6, C & E, Folic acid, zinc, iron);\(^\text{17}\) Enzyme preparations (trypsin, chymotrypsin, papain);\(^\text{18}\) Capsaicin; Licorice; Madonna lily; Reishi mushroom; Honey; Aloe.\(^\text{2}\)

XII. Prevention

In 1995, Varicella vaccine was recommended in USA for healthy children >1 year old, susceptible adolescents and also adults.\(^\text{1}\) In 2006, the FDA recommended a live attenuated vaccine derived from the oka strain of VZV for prevention of HZ and its complications.\(^\text{12}\) Since then a decrease of 90-95% of VZV infection in children aged 1-9 years was observed.\(^\text{4}\) It is safe, well- tolerated cost-effective and efficient. Protection by the vaccine remains for about 7 years.\(^\text{19}\)

A single 0.65 ml dose injected subcutaneously in the deltoid region.\(^\text{20}\) Vaccine cause an increase in cell-mediated immunity thereby causing a decrease in shingles and also decreased incidence of PHN.\(^\text{4}\) It also decreases the burden of illness.\(^\text{5}\) Studies have shown a decrease of 51.3% in incidence of HZ; 66.5% in incidence of PHN; 61% in BOI score.\(^\text{5}\) FDA recommends HZ vaccine for adults ≥ 50 years irrespective of person suffering with prior HZ episode.\(^\text{3}\) ACIP (Advisory Committee on Immunization Practices) has not applied any upper age limit for vaccine.\(^\text{3}\) Care should be taken to increase the vaccination coverage if zoster vaccine is given simultaneously with other vaccine.\(^\text{1}\) Several studies are being conducted on effects of inactivated VZV vaccine for immunosuppressed patients for who live attenuated vaccine is not recommended.\(^\text{3}\) Vaccine should be kept frozen at -15°C (once opened should be used within half an hour).\(^\text{3}\) FDA has approved transportation and storage at 2-8°C and up to 72 hours.\(^\text{20}\) Contraindications may include cases of life threatening hypersensitivity reactions, HIV patients with CD\(_4\) count <200. Patients on chemo/radiotherapy, Pregnancy and Breast feeding.\(^\text{3}\)

XIII. Conclusion

HZ though being a self-limiting condition, if left untreated can lead to various complications involving almost all the organs of human system, with PHN being the most critical one. However, an oral physician can be the first one to recognize the signs and symptoms thereby, being the first ones to make the initial diagnosis. Thus, dentists should have complete knowledge about the disease so that prompt treatment can be given and patient management can be done early and efficiently.

REFERENCES Références Referencias


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