A CLINICAL STUDY OF 100 CASES OF HERPES ZOSTER

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CERTIFICATE

Certified that this dissertation entitled ***"A CLINICAL STUDY OF 100 CASES OF HERPES ZOSTER"*** is a bonafide work done by **DR. C. CHANDRAKALA,** Post Graduate Student of the department of Dermatology, Venereology and Leprosy, Madras Medical College, Chennai – 600 003, during the academic year 2005 – 2008. This work has not previously formed the basis for the award of any degree.

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CONTENTS

INTRODUCTION

Varicella-Zoster virus (VZV) is the etiologic agent of two diseases, Varicella (Chicken pox) and Zoster (Shingles).

Varicella which occurs after the initial encounter with Varicella Zoster virus, is a disease manifested by a pruritic rash accompanied by fever and other systemic signs and symptoms that are usually mild to moderate nature.

Most often Varicella is a self-limited infection of childhood.

Zoster is mainly a disease of adults. A prerequisite for developing zoster is a prior episode of Varicella, which on occasion may have been sub-clinical.

During Varicella, VZV establishes latent infection in sensory nerve ganglion. Zoster results when the latent virus reactivates and returns from the ganglion to infect the skin.

Most often VZV reactivates in the settings of relative immunologic compromise, as occurs with aging, or following disease or various therapies, such as steroids, cancer chemotherapy transplantation and irradiation.

The diagnosis is clinical: very few other diseases mimic herpes zoster, especially in the localization of the rash, which is otherwise quite similar in appearance and initial effect of that of poison oak or poison ivy.

In case of doubt, diagnostic tests can be performed. Such lab tests may be necessary because, depending on the affected sensory nerve, the pain that is experienced before the onset of rash may be misdiagnosed as pleurisy, myocardial infarction, appendicitis or migraine headache.

A physician can take a viral culture of a fresh lesion, (or) perform a microscopic examination of the blister base material called a Tzanck preparation.

In a complete blood count, there may be an elevated number of white blood cells, which is an indirect sign of infection. There may also be a rise in the antibody to the virus, which could also give indication to the virus.

Currently, there is no complete cure available for herpes zoster, nor a treatment to effectively eliminate the virus from the body. However, there are some treatments that can mitigate the length of the disease and alleviate certain side effects.

REVIEW OF LITERATURE

HISTORICAL OVERVIEW:

Varicella was distinguished clinically from small pox in the mid 18th century. The origin of the name chickenpox is uncertain, but it may have been derived from the French “pois chiche” or chick pea or from the farmyard fowl (in old English cicen and Middle High German kuchen). The name ‘shingles’ is derived from the Latin word ‘cingulus’ meanings girdle (Zaia, 1981)

Herpes is derived from the Greek word meaning to “creep”.

Zoster is the Greek word meaning “girdle or belt”.

In 1875, Steiner successfully transmitted VZV by inoculation of the vesicular fluid from a person suffering from chickenpox to - “volunteer”[1].

The delineation of the link between Varicella and zoster is of virologic, medical and historical interest. A connection was postulated in 1888 by Von Bokay[2] who recognized that cases of Varicella often occurred following exposure to a patient with zoster.

Kundratitz in 1925[3] showed that the inoculation of vesicular fluid from patients with herpes zoster into susceptible person resulted in chickenpox. Similar observations were reported by Brunsguard and others.

In 1943 Garland[4] suggested that herpes zoster was the consequence of the reaction of latent VZV.

Since early in the 20th century, similarities in the histo-pathologic feature of skin lesions and in epidemiologic and immunologic studies indicated that Varicella and herpes zoster were caused by the same agent[5].

Tyzzer[6] described the histo-pathologic features of skin lesions resulting from VZV injections and noted the appearance of intranuclear inclusions and multinucleated giant cells.

The histopathologic descriptions were amplified by Lipschutz in 1921[7] for herpes zoster.

Isolation of VZV in 1958 permitted a definition of the biology of this virus[8].

By 1958, Weller and colleagues[8] had been able to establish that there were neither biologic nor immunologic differences between the viral agents isolated from patients with chickenpox and herpes zoster.

Viral DNA from a patient with chickenpox who subsequently developed herpes zoster was examined by restriction endonuclease analysis and the molecular identity of these two viruses was verified.

Hope-Simpson[10] was the first to recognize the importance of the immune system in controlling manifestations of zoster. He postulated that zoster resulted when humoral immunity to VZV wanes in the years and decades after Varicella.

More recently the importance of declining cellular rather than humoral immunity to VZV was recognized in the pathogenesis of zoster[10].

Cyto-diagnosis of herpes infection by smear taken from the base of a blister reveals the characteristic cytopathic effects of herpetic infection and multinucleated giant cells were introduced by Tzanck in 1947[11].

Before the availability of antiviral drug, oral pancreatic enzyme therapy in shingles was used in some countries and later subjected to clinical and scientific research[12]. A large scale study, using an oral preparation of such enzymes has shown promising results.

Antiviral drugs Acyclovir was discovered in 1974. Preclinical investigation brought the drugs to clinical trials in 1977 and the first form of drug (topical) was available in 1982[13].

A live attenuated vaccine using the same strain (Oka strain) as the Varicella vaccine, but at a much higher dose, proved its

efficacy in terms of reducing shingles and post-herpetic neuralgia incidences, of 51% and 67% respectively[14]. This vaccine received a marketing authorization in France for adults more than 60 years of age.

VIROLOGY:

Varicella – Zoster Virus

VZV is a member of the herpesviridae family and shares structural characteristics with other members of the family. The virus has icosapentahedral symmetry and contains DNA with a surrounding envelope. The size of the virus is approximately 150 to 200nm.

The nucleo capsid has a diameter of approximately 90 to 95 nm[15], consisting of 162 hexagonal capsomeres with central axial hollow organised as an icosahedron with 5:3:2 axial symmetry[16].

A biological important coat, the tegument, surrounds the nucleocapsid, which in turn is surrounded by an envelope that is derived in part from cellular membranes. The glycoproteins (gps) are termed I through VI. These glycoproteins have been the subject of intense investigative interest because they represent the primary markers for both humoral and cell mediated immune response.

VZV replicates in the nuclei of infected cells, where the DNA core and capsid are synthesized[17].

EPIDEMIOLOGY:

Herpes zoster is a disease that occurs at all ages, but it afflicts about 20% or more of the population overall, mainly the elderly[9]. The highest incidence of disease varies between 5 and 10 cases per 1000 for persons older than 60 years[18].

The incidence of zoster in children is low. Hope-Simpson[29] reported a rate of 0.74 per 1000 subjects per year in the age group 9. Guess[30] et al all noted that the rate increased from 20 cases per 1,00,000 person - years in the age group younger than 5 years to 63 cases per 1,00,000 person - years in the group aged 15 to 19 years.

Immunocompromised persons have a higher incidence of both chickenpox and shingles[19]. Both sexes are equally affected. Geographic and racial factors have been reported in studies of the epidemiology of Varicella and herpes zoster. Non – Caucasian racial group and tropical region people were each significantly associated with younger age at Zoster onset in a study conducted by Nagasako et al[21]. It is a sporadic disease occurring throughout the year. Contagiousness of infection from zoster patient is low, as secondary attack rate within household non-immune contacts is about 15%[22].

PATHOGENESIS:

Primary viraemia of VZV:

Airborne droplets are the usual route of transmission of primary Varicella (chickenpox). The incubation period ranges from 11 to 20 days. Varicella is extremely contagious with 80 to 90% of susceptible household contacts developing clinical infection.

VZV enters individual by infection of mucosal epithelial cells in the upper respiratory tract, oropharynx or conjunctiva. After primary replication in the epithelium, the virus is disseminated by the blood stream to the reticulo-endothelial system, where viral replication leads to secondary viremia. Infection of capillary endothelial cells allows spread of the virus to epithelial cells of the epidermis, where focal cutaneous lesions of Varicella are formed.

Host immunity limits the acute disease but during spread through the epidermal epithelium, the virus also infects sensory nerve endings and is transported to sensory ganglia. Latent infection is established in the ganglia, neurons and satellite cells[23].

LATENCY AND REACTIVATION:

VZV evades the immune response to establish latency in an immunological privileged site and down regulates gene expression

there. It is believed that latent infection is established in a host cell that is non permissive for viral gene transcription.

The configuration of VZV DNA in latently infected ganglia is extra chromosomal and circular[24]. Herpes zoster appears upon re-activation of VZV which may occur spontaneously or may be induced by stress, fever, radiation therapy, surgery, tissue damage or immune suppression[25].

During herpes zoster reactivation, the virus continues to replicate in the dorsal root ganglion and produces a painful ganglionitis. Inflammation and neuronal necrosis can result in severe neuralgia that intensifies as the virus spreads down the sensory nerve. If the existing immune response cannot control the re-activating virus, extensive viral replication can occur in the ganglia.

Virus also spreads to the periphery by axonal transport through neurons innervating a specific dermatome or dermatomes. There the virus productively infects the epithelium to cause the lesion characteristic of shingles[25].

HISTO - PATHOLOGY

SKIN LESIONS:

I. Early stage:

The earliest changes involve the epidermal cell nuclei which develop peripheral clumping of chromatin and a homogenous ground glass appearance, combined with ballooning of nucleus[26].

Vacuolization is the earliest cytoplasmic alteration. These changes begin focally along the basal layer, but soon involve the entire epidermis[26].

II. Vesicular Stage:

Intra epidermal vesicle results from two types of degenerative changes. 1). Ballooning degeneration & 2). Reticular degeneration.

Ballooning degeneration is peculiar to viral vesicles. The affected cells swell and loose their attachment to adjacent cells, thus separating from them (secondary acantholysis)[25].

The cytoplasm of these cells becomes homogenous and intensively eosinophilic and some are multinucleate (Tzanck cells) [11]. At times the basal layer of the epidermis is also destroyed in this way, leading to the formation of a sub-epidermal vesicle.

Reticular degeneration[25] is characterized by progressive hydropic swelling of epidermal cells, which become large and clear with only fine cytoplasmic strands remaining at the edge of the cells. These eventually rupture contributing further to the formation of a vesicle.

Whereas ballooning degeneration is found mainly at the base of the vesicle, reticular degeneration is seen on its superficial aspect and margin. Multinucleated giant cells containing upto 15 nuclei which are formed by fusion of epithelial cells containing eosinophilic intranuclear inclusion bodies (Lipschutz bodies, formerly Cowdry type A bodies)[27] of 3 to 8 mm in diameter.

III. Late stage:

Eosinophilic intra nuclear inclusion bodies are found, particularly in ballooned cells. Neutrophils are present within established vesicles. Neutrophilic and lymphocytic infiltration is also present in the underlying dermis. Marked inflammation and vasculitis[28] have been noted in some lesions. If the vasculitis is severe, necrotizing lesions will be present. Eccrine duct involvement has been reported. The chronic verrucous lesions show hyperkeratosis, verruciform acanthosis and virus-induced cytopathic changes[29].

IMMUNOLOGY

Both humoral and cell mediated immune responses to VZV develop within a few days after the onset of varicella.

Peak antibody levels are attained after 4 to 8 weeks; remain high for about 6 months and then decline. IgG Ab to VZV can be detected in healthy adults for decades after varicella[30]. After active immunization against varicella antibody titers are lower than after natural infection but persists for as long as 20 years in healthy children. Serum IgG, IgA and IgM develop after both varicella and zoster. Zoster occurs in the face of high levels of specific antibodies, but significantly higher titers develop during convalescence, reflecting an anamnestic response to this reactivation infection[31]. Antibodies seem to have an incomplete protective effect. Cellular immunity is thought to play the major role in host defense against VZV. Natural killer cells and antibody dependent cellular cytotoxicity against VZV have also been described. It is generally agreed that CMI, presumable T cell cytotoxicity is more important than humoral immunity in recovery from infection[32].

CLINICAL MANIFESTATIONS

Pre - eruptive Stage:

The first manifestation of zoster is usually pain, which may be severe and may be accompanied by fever, headache, malaise and tenderness localized to areas of one or more dorsal roots.

The time between the start of the pain and the onset of eruption averages 1.4 days in trigeminal zoster and 3.2 days in thoracic disease[33]. The skin in the affected area becomes red and papules soon develop[34]. Occasionally the pain is not followed by the eruption (zoster sine eruptione, zoster signe herpete)[35].

In the pre eruptive stage the pain simulates headache, eye pain, dental pain, pleurisy, brachial neuritis, cardiac pain, intra abdominal disease (especially gall bladder colic, appendicitis, renal colic, etc.) or sciatic syndrome. Prodromal symptoms may be absent, particularly in children[36].

ERUPTIVE STAGE:

Closely grouped red papules, rapidly becoming vesicular and then pustular develop in a continuous or interrupted band in the area of one, occasionally two and rarely more contiguous dermatomes.

Mucous membranes within the affected dermatomes are also involved. The lymph nodes draining the affected area are enlarged

and tender. Occasionally a few vesicles appear across the midline[36]. Rarely eruption may be bilateral.

Dermatome involvement in Herpes zoster:

Thoracic	-	53% (Commonest)
Cervical	-	20%
Ophthalmic	-	16%
Lumbosacral	-	11%

Possibly because chicken pox is centripetal (located on the trunk), the thoracic region is affected in two thirds of herpes zoster cases[36].

RESOLUTION STAGE:

The pain and constitutional symptoms subsides gradually as the eruption subsides, vesicles either umblicate or rupture before forming a crust, which falls off in 2 to 3 weeks.

In uncomplicated cases the recovery is complete in 2 to 3 weeks in children and young adults and 3 to 4 weeks in older patients[33].

CEPHALIC ZOSTER:

This includes involvement of cranial nerves, such as trigeminal nerve branches, facial nerve, auditory nerve, glossopharyngeal and vagal nerves.

TRIGEMINAL NERVE ZOSTER

It is due to involvement of Gasserian ganglion of the trigeminal nerve. Three branches of the trigeminal nerve such as ophthalmic, maxillary and mandibular divisions are affected by Herpes Zoster.

HERPES ZOSTER OPHTHALMICUS:

Herpes zoster ophthalmicus occurs when the recrudescence is in the ophthalmic branch of the trigeminal nerve. The ophthalmic involvement makes up to 10 to 15% of all cases of herpes zoster. V1 area involves forehead and upper eyelid. Infection involving the cornea with keratitis and uveitis and may lead to permanent damage. This presentation occurs when the nasociliary branch of ophthalmic division is involved and accordingly presents with cutaneous involvement of the nasal tip (Hutchinson's sign)[37].

Frontal sinusitis preceded 16% of all cases of ophthalmic zoster[38]. Patients with ophthalmic herpes zoster who are HIV negative tend to have less severe infection and also recover faster

than those who are HIV positive[39].Herpes zoster ophthalmicus is a known marker of HIV/AIDS in Africa[40].

HERPES ZOSTER OF MAXILLARY DIVISION OF TRIGEMINAL NERVE:

Zoster of maxillary division of the trigeminal nerve produces vesiculation of the tonsillar area, cheek, lower eyelid, side of the nose, upper lip as well as mucosa of nose, nasopharynx, palate, uvula and tonsillar area[41].

HERPES ZOSTER OF MANDIBULAR BRANCH OF TRIGEMINAL NERVE:

The dermal and mucous membrane distribution of this branch is to the side of the head, part of the external ear and external ear canal, lower lip, anterior part of the tongue, floor of the mouth and buccal mucous membrane. In oro facial zoster toothache may be the presenting symptom.

HERPES ZOSTER OTICUS/ RAMSAY-HUNT SYNDROME:

The facial nerve, mainly a motor nerve, has vestigial sensory fibres supplying the external ear (including pinna and meatus), tonsillar fossa and adjacent soft palate. Classical sensory nerve zoster in these fibres causes pain and vesicles in part or all of that distribution, though the skin involvement may be minimal and limited to the external auditory meatus.

Swelling of infected sensory fibres in their course through the confined spaces of the facial canal and the internal auditory meatus, leading to compression of adjacent facial nerve motor fibres resulting in facial palsy, which with the ear pain and associated vesicle completes the classic triad of Ramsay-Hunt syndrome[42].

Auditory nerve involvement occurs in 37.2% of patients resulting in hearing deficits and vertigo[43].

GLOSSOPHARYNGEAL AND VAGAL ZOSTER (HERPES PHARYNGITIS AND HERPES LARYNGIS) [62]:

This type involves the jugular and petrosal ganglia. Because these two ganglia are adjacent, they are often involved in some combination together but may be affected separately. The vesicular rash is likely to be on the palate, back of the tongue, epiglottis or faucial tonsils and occasionally in the external ear.

Palatal weakness, dysphonia, difficulty in swallowing, hyperesthesia in pharynx, loss of gag reflex, etc may occur. There is usually ear or deep pharyngeal or laryngeal pain.

HERPES OCCIPITOCOLLARIS (INVOLVEMENT OF C_2 AND C_3)[44]

The skin lesions seen over the back of scalp, back of neck, part of the ear and part of the lower jaw and front of neck. C_2 and C_3 are often involved together. There are communicating branches

of C_2 and C_3 with VII and X cranial nerves. Combinations of C2 and C3 with these cranial nerves are possible.

ZOSTER MENINGO ENCEPHALITIS:

This manifestation is most likely to be marked when cranial nerves (especially Trigeminal Nerve) are involved. This is because of a branch (recurrent nerve of Arnold) to the tentorium from ophthalmic branch of Trigeminal Nerve. Hence meningeal reaction (i.e. headache, changes in sensorium , fever, stiffness of neck , etc) is most common with herpes zoster ophthalmicus.

SACRAL ZOSTER (S_2, S_3 AND S_4 DERMATOMES):

A neurogenic bladder with urinary hesitancy or urinary retention[45] has reportedly been associated with zoster of the sacral dermatomes S_2, S_3 and S_4. Migration of virus to the adjacent autonomic nerves is responsible for these symptoms.

BILATERAL HERPES ZOSTER[46]

Herpes zoster is almost always unilateral. The rarity of bilateral cases is indicated by individual case reports in the literature.

HERPES ZOSTER WITH MULTIPLE UNILATERAL LESIONS[47]

This type is quite rare and most likely to be noted in persons with some severe systemic illness i.e. Hodgkin's lymphoma,

metastatic cancer, HIV, etc. Such diseases should be looked for when this dermal distribution is encountered.

RECURRENT HERPES ZOSTER[48]

Recurrent attacks are rare and zosteriform herpes simplex should always be ruled out[49].

ZOSTER IN MALIGNANCY:

Herpes zoster has been reported with Hodgkin's, lymphomas, leukemia, metastatic cancer and other neoplasm. The presence of Herpes zoster especially in an older person indicates the need for searching for these diseases as a causative background. Use of cytotoxic immunosuppressant therapy altering immune response may also be a factor.

HERPES ZOSTER IN HIV INFECTION

Herpes zoster is included in clinical stage - 2 of WHO staging system for HIV infection.

Herpes zoster occurring in HIV disease is usually typical in involving one or two adjacent dermatomes but uncommonly it may be multidermatomal, recurrent within the same dermatome or disseminated[50]. The eruption may be bulbous, hemorrhagic, necrotic and may be accompanied by severe pain.

The majority of HIV infected patients with herpes zoster experience an uneventful recovery; however atypical clinical course of herpes zoster is not uncommon[50]. Lesions may persist for months, either in localized or disseminated form, appearing as hyperkeratotic, ulcerated, painful nodules, often with central crusting or ulceration with a border of vesicles[51]. Systemic dissemination of herpes zoster with hepatitis, encephalitis and pneumonitis is common. HIV infected patients with herpes zoster show increased neurologic and ophthalmic complications particularly peripheral retinal necrosis[52]. Reactivation of varicella zoster virus is the commonest cutaneous manifestation of immune restoration disease[53].

HERPES ZOSTER IN CHILDREN

Herpes zoster in neonates and children may represent the result of an attenuated response to intra uterine or neonatal infection. Baba et al[54] reported that children who had varicella before 2 months of age has lower varicella zoster antibody titers and diminished skin test reactions; thus reactivation in these cases may be secondary to an abnormal immune response to the primary infection by varicella.

The development of herpes zoster is often preceded by radicular pain and is less common in children. Malaise, headache

and fever may precede the rash, particularly in younger patients. Resolution of lesion occur within 1 to 3 weeks.

Both normal and immunosuppressed patients may have generalization of herpes zoster. Post herpetic neuralgia is uncommon in children. Immunocompromised children with herpes zoster may have more extensive involvement with a higher risk of viremia and visceral dissemination.

HERPES ZOSTER IN PREGNANCY:

Herpes zoster during pregnancy, whether it occurs early or late in the pregnancy, appears to have no deleterious effects on either the mother or infant[55]. Maternal zoster in pregnancy is not associated with intra uterine infection[56]. But maternal Varicella in the first 20 weeks of pregnancy is associated with a approximate 2% risk of fetal damage[57].

COMPLICATION

1. Acute complications of herpes zoster:

Acute complications occur during the course of illness and are more common in immunocompromied individuals.

i. Cutaneous Complications

The common cutaneous complications are secondary bacterial infections, cutaneous necrosis, scarring, dissemination and gangrene formation.

ii. Ocular Complications[58]

Ocular complications include uveitis, keratitis, conjunctivitis, conjunctival edema, ocular muscle palsies, proptosis, scleretis, retinal vascular occlusion and ulceration, scarring and even necrosis of the lid. Involvement of ciliary ganglion may give rise to Argyl-Robertson pupil.

Acute retinal necrosis caused by Varicella-zoster virus occasionally occurs in immuno-competent patients, although more recent studies have focused on ocular disease in HIV infected patients[59].

iii. *Neurological Complications:*

This includes cranial neuritis, motor neuropathy autonomic neuropathy, aseptic meningitis, meningo-encephalitis, transverse myelitis[60], necrotizing myelopathy, Guillain-Barre Syndrome, hemiplegia and granulomatous angiitis.

a) Cranial Neuritis:

Cranial neuritis includes trigeminal nerve zoster (Herpes zoster opthalmicus, maxillary and mandibular nerve zoster),

Ramsay-Hunt syndrome with involvement of facial nerve and 8th cranial nerve, vagus and glossopharyngeal nerve zoster.

b) Motor Neuropathy:

This occurs overall in 5% of cases and is more common in older patients and those with malignancy and in cranial when compared with spinal nerve involvement. The motor weakness usually follows the pain and the eruption by a few days to a few weeks, but occasionally precedes or accompanies them. The affected segment is usually but not always the same. Complete recovery is expected in 55% and significant improvement in a further 30% of cases. In ophthalmic zoster, ocular palsies occur in 13% and facial palsies in 7%[61]. An abdominal hernia followed zoster involving thoracic 10th and 11th motor roots[62]. zoster of ano-genital area may be associated with disturbances of defecation or urination[63]. Herpes zoster oticus accounts for about 10% of cases facial palsy[64]. Glossopharyngeal[65] and vagal zoster[66] produces pharyngeal and palatal muscle weakness. Zoster of the second to fourth cervical nerves may paralyze the ipsilateral diaphragm due to involvement of the phrenic nerve.

c) Autonomic Neuropathy:

Autonomic nervous system may also be affected. Autonomic nerve involvement often presents as bladder dysfunction. Gastro-intestinal tract involvement presents as spasm, hypotonia or ileus.

d) Herpes zoster Meningo - encephalis

Neurologic symptoms characteristically appear within the first 2 weeks of onset of the skin lesions. Patients at risk are those with trigeminal and disseminated zoster as well as the immunosuppressed. Rarely manifestations of a meningo-encephalitis may be significant and at times severe enough to cause death.

e) Granulomatous angiitis[67] (or) Delayed contra-lateral hemiparesis:

By direct extension along the intracranial branches of the trigeminal nerve, VZV gains access to the CNS and infects the cerebral arteries. Patients present with headache and hemiplegia.

f) Herpes zoster Myelitis:

More rarely, the myelitis lesion predominates in zoster or is the sole feature, so the clinical picture is one of acute onset of paraplegia from a diffuse involvement of the spinal cord. The picture is that associated with acute transverse myelopathy.

iv. Visceral Complications:

Patients with lympho-proliferative malignancies are at risk for cutaneous dissemination and visceral involvement, including Varicella pneumonitis, hepatitis and meningo-encephalitis.

2. Complications occurring after resolution of Herpes Zoster lesions:

i. Post Herpetic Neuralgia

The commonest and most intractable sequel of zoster is Post-herpetic neuralgia, generally defined as persistence or recurrence of pain for more than a month after the onset of zoster, but better considered after 3 months. It occurs in about 30% of patients over 40 years of age and is most frequent when trigeminal nerve is involved[68].

The pain has two main forms, a continuous burning pain with hyperaesthesia and spasmodic shooting type, although a pruritic "crawling" paraesthesia may occur. Allodynia, pain caused by normally innocuous stimuli, is often the most distressing symptom and occurs in 90% of people with post herpetic neuralgia[68].

Patho-physiology of pain

A number of different overlapping mechanisms appear to be involved in the pathogenesis of pain in herpes zoster and post herpetic neuralgia[68].

Injury to the peripheral nerves and to neurons in the ganglion triggers afferent pain signals. Inflammation in the skin triggers nociceptive signals that further amplify cutaneous pain. The abundant release of excitatory aminoacids and neuro-peptides induced by the sustained barrage of afferent impulses during the prodrome and acute phase of herpes zoster may cause excito-toxic injury and the loss of inhibitory inter-neurons in the spinal dorsal horn.

ii. Post Herpetic Itch[69]:

Many patients with shingles experience neuropathic itch accompanying pain or itch may be present instead of pain.

iii. Progressive multifocal leuko-encephalopathy

In addition to latent infection, VZV can produce prolonged smouldering sub-clinical infection in patients lacking normal defenses to eliminate the viral infected cells and resulting in cell to cell spread of infection.

iv. Scarring:

Elderly, malnourished, debilitated or immuno-suppressed patients tent to have a more virulent and extensive course of disease and Scarring. Sometimes keloidal or hypertrophic scars follows herpes zoster.

v. Inflammatory skin lesions following a zoster infection (Isotopic Response)

Following zoster, inflammatory skin lesions may rarely occur within the affected dermatome. Lesions usually appear within a month and rarely, longer than 3 months after zoster.

Lesions reported in herpes zoster scar include a keloid, comedones, lichen planus, giant cell lichenoid dermatitis, urticaria, granulomatous vasculitis, granulomatous folliculitis, sarcoidosis, lichen sclerosis et atrophicus, morphoea, eosinophilic dermatosis, fungal infections, pseudolymphoma, lymphoma, leukemia cutis, Rosai-Dorfman disease, Kaposi's sarcoma, various skin cancers and metastasis[70].

DIAGNOSIS OF HERPES ZOSTER

CLINICAL DIAGNOSIS

The diagnosis is largely clinical. Grouped vesicles of varying sizes on an oedematous and erythematous base with skipped areas of normal skin in a dermatomal distribution makes the diagnosis of herpes zoster, quiet obvious most of the times.

INVESTIGATIONS:

1. Morphological test

Tzanck Smear:

The initial test of choice is a cytological smear (Tzanck smear). The test does not differentiate herpes simplex from varicella. The base of an early lesion is scraped and stained with haematoxylin and eosin, Giemsa, Wright's stain, toluidine blue or papanicolaou stain. Multinucleated giant epithelial cells and epithelial cells containing acidophilic intranuclear inclusions are seen.

2. Skin Biopsy:

Histo-pathological appearances of herpes simplex, varicella and herpes zoster are very similar. Ballooning degeneration is peculiar to viral vesicles. Whereas ballooning degeneration is found

mainly at the base of the vesicle, reticular degeneration is seen on its superficial aspect and margin.

3. Virological Investigations:

a) Viral Culture:

The most definitive test is a positive viral culture from vesicular fluid, but a minimum of 48 to 72 hours is required to produce the diagnostic cytopathic effects. Infective material is inoculated into human amnion, human fibroblast, HeLa[71] or Vero cells.

b) Varicella zoster virus antigen detection:

VZV antigen may be demonstrated by immunoflourescence, using a commercially available monoclonal antibody to VZV that is conjugated to flourescin[72].

c) Electron Microscopy:

The ultra-structural features of Varicella zoster virus are similar to those of Herpes simplex virus. However colloidal gold immuno-electron microscopy using monoclonal antibodies can distinguish between the two conditions[73].

4. Serological Tests:

A number of sensitive serologic tests are available to measure antibodies to VZV)

Serologic tests include

1. Fluorescent antibody to membrane antigens (FAMA)
2. Latex agglutination test
3. Enzyme linked immunosorbent assay (ELISA)
4. Enzyme Immuno assay (EIA)
5. Immune adherence haemagglutination assay (IAHA)
6. Radio Immuno assay (RIA)
7. Complement fixation test (CFT)
8. Varicella zoster virus neutralization tests.

5. Newer Techniques:

i. Nucleic acid probes

The nucleic acid hybridization test has also been described for the detection of Varicella zoster virus DNA sequences in clinical specimens. The spot hybridization assay used was comparable to cell culture in sensitivity and specificity.

ii. Polymerase Chain Reaction:

PCR is more sensitive than viral culture or Tzanck smear for detecting VZV infections. PCR was described as particularly useful for the rapid and specific diagnosis of VZV infections without the practical and technical limitations of conventional viral isolations or Tzanck smears[74].

TREATMENT

The aim of treatment is the suppression of inflammation, pain and infection.

TOPICAL TREATMENT:

During acute phase of herpes zoster, the application of wet compresses, calamine lotion, Burrow's solution cornstarch, or baking soda may help to alleviate local symptoms and hasten the drying of vesicular lesions.[75]

Topical Acyclovir

Topical treatment of herpes zoster rash with antiviral agents is not effective[75]

Systemic Therapy

The major goals of therapy in patients with herpes zoster are to limit the extent, duration and severity of pain and rash in the primary dermatome and to prevent disease elsewhere and PHN.

SYSTEMIC ANTIVIRAL AGENTS

1. ACYCLOVIR

Oral acyclovir significantly reduced the healing time, duration of viral shedding and acute pain in randomized controlled trials in patients older than 50 years of age who were treated within

72 hours of rash onset[76]. Aciclovir is a guanosine analogue and is widely used for the treatment of HSV and VZV infections.

MECHANISM OF ACTION:

The active antiviral moiety aciclovir is aciclovir triphosphate, which is a potent inhibitor of certain herpesvirus induced DNA polymerases, but has relatively little effect on host cell DNA polymerase.

INDICATIONS AND DOSAGE:

Varicella zoster virus is less sensitive to aciclovir than HSV, higher doses of the drug should be used.

ORAL:

Indications:

1. Immunocompetent persons with age 50 years or above[25].
2. Immunocompetent patients with ophthalmic zoster.
3. Localised zoster (one or two dermatome) in asymptomatic HIV positive patients[77].

Dosage:

800 mg 5 times a day (in adults) or 20 mg/kg every 6 hours (in children) for 7 days in immunocompetent individuals and 10 days for immunocompromised.

INTRAVENOUS ACICLOVIR:

1. Disseminated or localized zoster involving more than 3 dermatomes in immunocomprised patients.

2. Chronic, severe zoster in advanced AIDS patients[77].

3. Zoster involving cranial nerves with complications such as Ramsay - Hunt Syndrome[25] or Ophthalmic zoster in HIV patients[77].

4. Visceral dissemination[25].

5. Localised zoster in HIV positive patients with impaired intestinal function (i.e. diarrhea or malabsorption) where intravenous route is preferred to ensure adequate drug level.

6. Herpes Zoster encephalitis

Dose: 500mg/m^2 in children or 10mg/kg body weight in adults, infused over one hour at every 8 hours for 7 to 10 days.

2. VALACYCLOVIR:

It is the L-valine ester of aciclovir. It was developed to provide increased oral bioavailability of aciclovir[78]. Valacyclovir may be more effective in resolution of zoster associated pain[79]. Dose: 1 gm tds for 7 days.

3. FAMCICLOVIR AND PENCICLOVIR:

Famciclovir is a prodrug of pencilovir. Penciclovir is phosphorylated to penciclovir triphosphate. Penciclovir triphosphate inhibits viral DNA polymerases and also inhibits extension of the nascent viral DNA chain[80]. Dose: Farmciclovir 500mg tid for 7 days.

4. FOSCARNET (TRISODIUM PHOSPHONOFORMATE)

It is a pyrophosphate containing compound that is active in vitro against varicellar zoster virus. Forcarnet noncompetitively inhibits viral DNA polymerases at the pyrophosphate binding[81] sites.

Dosage:

Initial dosage of 40 to 60mg / kg administered intravenously, 8th hourly for 14 to 21 days followed by a maintenance dose of 120mg/kg/day.

5. CIDOFOVIR:

It is a phosphonate nucleotide analogue. It has activity against a broad range of herperviruses.

Cidofovir does not require initial phosphorylation by virus induced kinases, but is converted by host cell enzymes to cidofovir diphosphate which is a competitive inhibitor of viral DNA polymerases and to a lesser extent of host cell DNA polymerases.

6. VIDARABINE (ADENINE ARABINOSIDE)

It is an adenosine analogue which is phrosphorylated intracellularly by host enzymes and rapidly metabolised to hypoxanthine arabinoside by adenosine deaminase, resulting in markedly reduced antiviral activity within the cells. This instability and systemic toxicity have limited its use[82]. Dose: 10mg/kg/day infused over 12 hours for 5 days.

7. IDOXURUDINE

This synthetic nucleoside is effective against DNA viruses, particularly the herpes group. Its use is now restricted to topical application because of severe bone marrow and hepatic toxicity when given intravenously.

RECENT DRUGS:

(1) Sorivudine:

It is an uracil analogue with activity against VZV infections. It requires viral thymidine kinase for phosphorylation.

(2) Brivudine:

It is a new uracil derivative with potent and specific activity against VZV. It is effective in a single or twice daily dose orally (50 to 200 mg) in immunocompetent adults and older patients [83]. In immunocompromised patients, it is as effective as iv aciclovir in the dose of 125mg tablet every 6 hours.

(3) Oral enzyme therapy:

Oral enzyme therapy is beneficial in diseases characterized in part by TGF-β over production that included slingles patients[84].

(4) Human Interferon-A

Interferons are synthesized by DNA recombinant technology. Is nonspecific antiviral effects, involving synthesis of RNA and additive protein, with immunomodulatory effects, help in preveting VZV synthesis and elimination of infected cells.

ROLE OF STEROIDS IN HERPES ZOSTER MANAGEMENT:

Combination therapy of steroid and aciclovir resulted in an improved quality of life, as measured by reductions in the use of analgesics, the time to uninterrupted sleep, and the time to resumption of usual activities[85]. However, neither study demonstrated any effect of corticosteroids on the incidence or duration of post herpetic neuralgia.

Treatment of acute pain associated with herper zoster:

For acute pain scheduled short acting narcotic analgesics should be prescribed. For persistent pain, long acting, controlled - release opioids are preferred. If pain control remains inadequate then regional or local anesthetic nerve blocks should be considered. The effectiveness of carefully managed opiates, and tricyclic antidepressants during the acute phase of herpes zoster in reducing the incidence, duration of severity of PHN is not known. Intradermal steroids, xylocaine and epinephrine can also be given.

TREATMENT OF POST HERPETIC NEURALGIA:

TOPICAL THERAPY:

1. Topical lidocaine patch[86]
2. Topical EMLA cream
3. Topical Capsaicin (0.025%)cream
4. Topical aspirin tablets in chloroform[33]

5. Doxepin cream (5%)[88]

SYSTEMIC TREATMENT

1) Anticonvulsants

For stabbing pain, sodium valproate, clonazepam, carbamazepine and Gabapentin are effective.

2) Tricyclic antidepressants:

Desipramine. nortriptyline, maprotiline, Amitriptyline, are effective in post herpetic neuralgia. They are thought to act independent of their antidepressant actions.

(3) Oxycodone:

controlled release oxycodone (10mg every 12 hours) is an effective analgesic for the management of steady pain, paroxysmal spontaneous pain and allodynia.

(4) Analgesics:

Aspirin and other non steroidal anti inflammatory drugs are commonly used in patients with post herpetic neuralgia, but their value is limited. Tramodol[87], a centrally acting analgesic with opioid and non opioid activities also effective in post herpetic neuralgia (maximum dose 600mg / day)

(5) Anti psychotics

Fluphenazine, chlorprothixene, and perphenazines are used with other drugs.

OTHER MODALITIES OF TREATMENT:

1. Intrathecal methyl Prednisolone
2. Intradermal steroids, xylocaine and epinephrine injection.
3. Sympathetic blocks (stellate ganglion or epidural) with 0.25% bupivacaine prevents or relieves post herpetic neuralgia. Epidural injection are made at or just above the highest dermatome of the rash.
4. TENS (Transcutaneous electrical nerve stimulation) may be helpful.
5. Acupuncture[25]
6. Spinalcord stimulators.
7. Bio feed back[25]
8. Jaipur block[89]

   This consists of local subcutaneous infiltration of 2% lignocaine, 0.5% bupivacaine, and 4mg /ml dexamethasone, 2.5 ml each taken in a syringe and from which 4 to 5 ml of clear solution is given blindly at

about 4 to 10 sites in one sitting. By this method, reported from India, 28% reported complete relief at 6 weeks, 57% after second injection and 11% after third injection[89].

SURGICAL PROCEDURES

1. Division of dorsal root / tracotomy.
2. Rhizotomy (surgical separation of pain fibres)
3. Electrocoagulation of well defined area of dorsal root[89].
4. Electrical stimulation of thalamus and spinal cord.
5. Anterolateral cordotomy[89].

PREVENTION OF HERPES ZOSTER

(Zoster vaccine live (oka /merck)[90]

A subcutaneously administered live high titre (18,700 to 60,000 plaque -forming units per dose) varicella-zoster virus vaccine (zoster vaccine) of the oka/ Merck strain has been evaluated for the prevention of hesper zoster and the reduction of zoster associated pain in adults aged 60 years or above.

AIMS OF THE STUDY

The study of herpes zoster was undertaken to findout:

1. Age incidence
2. Sex Incidence
3. Prevalence of prodromal symptoms
4. Predominant complaints given by patients.
5. Prevalence of constitutional symptoms.
6. Pattern of dermatomal involvement.
7. Prevalence of association with HIV.
8. Association with cutaneous disease, if any.
9. Association with systemic disease, if any.
10. Duration of time taken for resolution of lesions.
11. Prevalence of complications.

MATERIALS AND METHODS

The study was conducted between July 2005 and July 2007 at the department of Dermatology, Madras Medical College, Chennai, on hundred cases of herpes zoster. All cases of herpes zoster attending skin out patient department and referred cases of zoster from other departments were studied.

Patient's age, sex, occupation, and address were noted. A detailed history regarding the prodromal symptoms, skin lesions, nature of pain, duration of illness at the time of presentation, provocative factors were recorded. Associated cutaneous disease, systemic disease and HIV infection were recorded. History of chicken pox and previous attack of zoster were elicited and time taken for complete resolution of lesions were noted. Complications of herpes zoster and association with HIV were also recorded.

Each patient underwent detailed general physical and systemic examinations. A thorough dermatological examination was done in all cases and the following details were noted.

1. Site of lesion (segment involvement)

2. Morphology of lesions like grouped vesicles, scattered vesicles, erythema, papules, erosions and crusting.

3. Dermatomal distribution & the side of involvement.

4. Cutaneous dissemination.

5. Lymph node enlargement.

6. Mucosal lesions.

7. Motor zoster

8. Other cutaneous diseases.

The diagnosis of herpes zoster was made clinically on the basis of characteristic presentation of vesicles in dermatomal or disseminated pattern. Diagnosis was confirmed with Tzanck smear and skin biopsy whenever required. A set of laboratory investigation consisting of complete hemogram, blood sugar, renal function test, urine analysis, ELISA for HIV antibody were done in all cases. Whenever necessary, other specialist's opinions like ophthalmologist, physician, neurologist and diabetologist were sought.

All patients were treated with oral aciclovir. Systemic antibiotics were given for cases with secondary bacterial infection and erosions. Patients with intractable zoster pain were given carbamazepine or amitriptyline and analgesics. In addition to systemic therapy, topical soothening agent like zinc oxide -

calamine lotion, or topical antibiotic creams were given. These patients were assessed with regards to the course of the disease, resolution time, pain relief and complications.

All the patients were reviewed every 4 days, until the time of complete healing. After that patients were followed once weekly or more frequently depending upon the cases and complications encountered till the resolution of problems.

During the follow up period the following complications were noted.

1. Secondary bacterial infection.
2. Dissemination
3. Ulceration
4. Delayed healing
5. Post inflammatory hypo or hyperpigmentation.
6. Scarring
7. Post herpetic neuralgia.
8. Other complications, if any.

OBSERVATIONS

AGE AND SEXWISE PREVALENCE OF ZOSTER

Table - I

S.No	*Age Group*	*Male*	*Female*	*Total no. of cases*	*Percentage*
1.	1-10	Nil	1	1	1%
2.	11-20	6	3	9	9%
3.	21-30	17	8	25	25%
4.	31-40	12	2	14	14%
5.	41-50	18	6	24	24%
6.	51-60	6	5	11	11%
7.	61-70	11	3	14	14%
8.	71-80	1	-	1	1%
9.	81-90	1	-	1	1%
	Total	72	20	100	

Out of 100 cases 72 were males and 28 were females.

Age wise distribution (Table-1) shows that 73 cases were below the age of 50 and 27 were above the age of 50 years.

Maximum number of cases were seen between the age group of 21 to 30 years (25%) and 41 to 50 years (24%) which was followed by 31 to 40 years (14%) and 61 to 70 years (14%). Minimum number of cases were observed in the age group of 1 to 10 years (1%), 71 to 80 years (1%) and 81 to 90 years (1%).

The youngest was 9 years and oldest was 81 years of age.

Out of 100 cases, 72 were males and 28 were females and the sex ratio is 2.5: 1 (male: female) approximately.

2. PREVALENCE OF PRODROMAL SYMPTOMS

The following prodromal symptoms were recorded.

1. Fever and pain
2. Dermatomal pain
3. Burning sensation
4. Itching
5. Tingling, numbness, paraesthesia
6. Ear pain
7. Tooth ache
8. Erythema

Prodromal symptoms were present in 85 cases and absent in 15 cases. Dermatomal pain prior to the onset of lesions was the commonest prodromal symptom (57%). The next common prodromal symptom seen was burning sensation (10%). Fever and pain was present in 6% of cases. Itching was present in 4% of cases. Ear pain and tooth ache were present in one case of herpes zoster oticus and one case of mandibular nerve zoster respectively.

Table -2 : Prevalence of prodromal symptoms

S.No	*Prodromal Symptom*	*Total no. of cases*	*Percentage*
1.	Dermatomal pain	57	57%
2.	Fever and pain	6	6%
3.	Burning Sensation	10	10%
4.	Itching	4	4%
5.	Tingling, numbness, paraesthesia	4	4%
6.	Ear Pain	1	1%
7.	Tooth Ache	1	1%
8.	Erythema	2	2%
9.	Absence of prodromal symptoms	15	15%

3. DURATION OF ILLNESS AT THE TIME OF PRESENTATION TO THE HOSPITAL:

Out of 100 cases, 74% of cases presented with vesicular lesions within 5 days of onset of lesions. The remaining 26% of cases were presented after 6 days and above to the hospital. The complications like secondary infection and PHN were maximum in those cases came for treatment late in the course of the disease.

Table - 3: Duration of illness at the time of presentation

S.No	*Duration of illness*	*Total no. of cases*	*Percentage*

1.	2 days	18	18%
2.	3 days	20	20%
3.	4 days	26	26%
4.	5 days	10	10%
5.	6 days	4	4%
6.	7 days	12	12%
7.	8 days & above	10	10%
		100	

4. PREVALENCE OF PRESENTING COMPLAINTS AND CONSTITUTIONAL SYMPTOMS

Most common presenting complaint was pain in 99% of cases. In 57% of cases pain was present prior to the onset of lesions and the remaining 42% of cases developed pain during evolution of vesicles.

Vesicular lesion was the next common presenting complaint in 98% of cases and it was present in association with pain in almost all cases.

Other presenting complaints were erosions, crusting, itching and burning sensation in very few cases (1 to 2 %). Headache and watering in the eye were present in 6 % of cases of ophthalmic zoster. Facial palsy was the presenting complaint in 1% of case.

Fever was the most common constitutional symptoms present in 45% of cases other constitutional symptoms present with fever were myalgia (18%), headache (12%) and joint pain (2%).

5. MORPHOLOGY OF LESION AND PATTERN DERMATOME INVOLVEMENT:

Grouped vesicles with erythematous background in dermatomal distribution were present in 97% of cases. The remaining 3% of cases had crusting and erosion alone. Other lesions presented with grouped vesicles were pustules, erosions and crusting. Oral erosions were seen in 2% of cases of maxillary and mandibular nerve zoster.

Redness of eyes and eyelid edema were present in 6% of cases of ophthalmic zoster.

Thoracic dermatome was the most common dermatome involved (60%) followed by cervical in 9% of cases, ophthalmic zoster in 8% of cases and lumber segment in 7% of cases.

The prevalence of maxillary, mandibular and herpes zoster oticus was 2% each.

Thoracolumbar and cervicothroracic involvement was 6% and 3% respectively. The least common dermatome involved was sacral dermatome (1%)

The pattern of dermatome involvement was almost similar in both sexes.

Dermatome involvement was predominantly on the left side (52%) when compared to right side (48%). But in lumbar, cervical and opthalmic zoster right side was commonly involved.

Table-4 : Pattern of dermatome involvement:

S.No	Dermatome	Sex		Side		No. of cases	Percentage
		Male	Female	Left	Right		
1.	Thoracic	47	13	36	24	60	60%
2.	Lumbar	4	3	1	6	7	7%
3.	Cervical	5	4	2	7	9	9%
4.	Sacral	0	1	1	0	1	1%
5.	Thoraco Lumbar	5	1	3	3	6	6%
6.	Cervico thoracic	1	2	1	2	3	3%
7.	Ophthalmic	7	1	3	5	8	8%
8.	Maxillary	1	1	1	1	2	2%
9.	Mandibular	1	1	2	0	2	2%
10.	Herpes zoster oticus	1	1	2	0	2	2%
	TOTAL CASES	72	28	52	48	100	

6. MULTIDERMATOMAL INVOLVEMENT AND DISSEMINATION

Multidermatomal involvement was noted in a case of herpes zoster oticus. The affected patient was an elderly man (70 years) with carcinoma prostate. He had involvement of C2, C3 and C4 segment in addition to herpes zoster oticus with facial palsy on the left side.

Cutaneous dissemination was noted in 2 cases in addition to the classical dermatomal distribution of grouped vesicles. One patient was a 36 year old male with HIV infection and another patient was a 65 year old male with no underlying immunosuppression or malignancy.

No recurrence of herpes zoster was observed in any case.

7. LYMPH NODE ENLARGEMENT:

Regional lymph node enlargement was noted in 95% of cases. Nodes were tender in 80% of cases and non tender in 15% of cases and are firm in consistency. Generalised lymphadenopathy (PGL) was present in twelve HIV positive cases.

8. PROVOCATIVE FACTORS:

Out of 100 cases, 36 cases were having one or more suspected provocative factors. Among the 36 cases, 16 cases (44.4%) were having HIV, 7 cases (19.4%) were having diabetes and 5 cases (13.8%) were on steroid therapy for SLE (3 cases) and bronchial asthma (2 cases).

Table - 5

PREVALENCE of provocative factors

S.No.	*Provocatve Factors*	*Male*	*Female*	*Total*	*%*
1.	HIV	14	2	16	44%
2.	Physical Stress (Parturition)	0	1	1	2.7%

3.	Diabetes	6	1	7	19.4%
4.	Renal transplantation	1	0	1	2.7%
5.	Steroid therapy	2	3	5	13.8%
6.	Hansen's disease	1	0	1	2.7%
7.	Pulmonary Tuberculosis	1	0	1	2.7%
8.	Pregnancy	0	1	1	2.7%
9.	Radiotherapy	0	2	2	5.5%
10.	Malignancy (Prostate cancer)	1	0	1	2.7%
	TOTAL	**26**	**10**	**36**	

Hansen's disease and tuberculosis were also present in 2 cases of herpes zoster. Physical stress of parturition was suspected as a provocative factor of zoster in a case of postpartum female. Immunosuppression of pregnancy was the probable cause for zoster in an antenatal case (2.7%).

A renal transplant patient (2.7%) on azathioprine therapy developed herpes zoster. Two female patients on radiotherapy for carcinoma breast and carcinoma cervix had herpes zoster (5.5%).

One male patient (2.7%) with carcinoma prostate developed multidermatomal herpes zoster with herpes zoster oticus.

Among the 16 HIV positive cases 14 were males and 2 were females.

9. PAST HISTORY OF CHICKEN POX:

Table-6 : Age group - wise past history of Chicken Pox

S.No.	*Age Group*	*Male*	*Female*	*Total*	*%*
1.	1-10 years of age	23	8	31	31%
2.	11-20 years of age	22	10	32	32%
3.	H/o. chicken pox in childhood (exact age not known)	18	9	27	27%
4.	No history of chicken pox	9	1	10	10%
	Total	72	28	100	

Out of 100 cases, 90% gave definite history of occurrence of chicken pox out of 90 cases. 27% of patient did not give the exact age of occurrence of chicken pox. 32% of cases gave history of chicken pox between 11 to 20 years of age and 31% of cases gave history of vericella between 1 to 10 years. The remaining 10% of cases were either not aware of or not had chicken pox at all.

10. ASSOCIATED CUTANEOUS AND SYSTEMIC DISEASES:

Cutaneous diseases seen in association with herpes zoster were acne 1 case, seborrhoeic dermatitis two cases, tinea versicolor 2 cases, SLE 3 cases, Hansen‘s disease 1 case, insect bite allergy 2 cases, wart 1 case, cellulitis 1 case, oral candidiasis 1 case, tinea cruris 1 case and intertrigo 1 case. Most of these cases were seen in association with immunosuppression.

Diabetes (7 cases) was the most common systemic disease seen in association with herpes zoster. The next common systemic disease seen with zoster was hpertension (6 cases). Other systemic diseases seen with herpes zoster were SLE (3 cases), bronchial asthma (2 cases), tuberculosis (1 case), Hepatitis B (1 case) and chronic renal failure (1 case).

11. TIME TAKEN FOR RESOLUTION OF LESIONS:

Most cases (50%) showed complete resolution of lesions between 15 to 21 days (3rd week). All patients were given T. aciclovir 800mg 5 times a day for 8 days except for immunocompromised patients and they were given aciclovir for 10 days. The response to aciclovir was good and resolution was rapid unless there was secondary bacterial infection or underlying immunosuppression.

Table - 7 : Resolution time of zoster lesions

S.No.	*Duration*	*No. of cases*	*%*
1.	8 to 14 days	35	35%
2.	15 to 21 days	50	50%
3.	22 to 28 days	14	14%
4.	29 days and above	1	1%

Resolution of lesions occurred within 8 to 14 days (2 weeks) in 35% of cases and in the range of 22 to 28 (wihtin 3 weeks) days

in 14% of cases. One case with underlying immunosuppression and necrotic lesion resolved at 29 days.

12. INVESTIGATIONS:

Complete hemogram was within normal limits except for increasecd eosinophil count in 6 patients, increased ESR in 20 patients, increased neutrophil count in 6 patients, decreased haemoglobin value in 4 patients.

Blood sugar was elevated above the normal valve in 7 patients. Urine routine examination was normal in almost all patients (98%). Urine examination showed reducing sugar in 2 patients with elevated blood glucose value.

ELISA test for HIV antibody was done in all patients. Positive ELISA test result was obtained in 6 cases. 10 patients were already diagnosed as HIV Positive and presented with zoster during the course of HIV disease

ECG was taken for patients with zoster involving left thoracic segment and it was found to be normal.

One patient with SLE had elevated blood urea and serum creatinine values and nephrologist opinion obtained for her and she was diagnosed as a case of SLE nephropathy.

Diabetologist opinion for 3 patients, neurologist opinion for 13 patients, ophthalmologist opinion for 8 patients and ENT surgeon opinion for one case of herpes zoster oticus were obtained.

Tzanck smear was positive in 95% of cases and negative in 5% of cases who presented late and those with ulcerations, erosions and crusting.

Skin biopsy was done in 2 patients with erythematous plaques studded with very few grouped papules in a dermatomal pattern, in the pre eruptive stage, which under light microscope in haematoxylin and eosin staining showed intraepidermal uniloculated to multiloculated bullae with ballooned epithelial cells and multinucleated giant cells. Reticular degeneration seen in some areas. The upper dermis showed inflammatory infiltration.

13. COMPLICATIONS:

a. Secondary bacterial infection:

Secondary bacterial infection was reported in 15 cases (37.5%). In 2% of patients with secondary infection scarring occurred in affected dermatome. Cases were treated with topical silver sulphadiazine cream and systemic antibiotics in addition to aciclovir.

b. Scarring:

Scarring was noted in 5 cases (12.5%) out of 5 cases, 3 cases had erosions and ulcerations of the lesion and 2 cases were associated with secondary bacterial infection and later developed ulceration.

c. Motor Zoster:

Facial palsy was seen in a patient (2.5%) with Ramsay Hunt Syndrome with underlying prostatic carcinoma.

Table - 8

PREVALENCE OF COMPLICATIONS

Complication	*M*	*F*	*T*	*Percentage*
Scarring	5	0	5	12.5%
Secondary bacterial infection	12	3	15	37.5%
Post herpetic neuralgia	14	5	19	47.5%
Motor Zoster	1	0	1	2.5%
TOTAL	32	8	40	

d) Post herpetic neuralgia:

PHN is the most feared complication in immunocompetent patients. Both the incidence and duration of post herpetic neuralgia are directly correlated with the patient's age. Out of 40 patients with complications of zoster, 19 cases (47.5%) developed post herpetic neuralgia.

Among the 19 cases of post herpetic neuralgia, 14 were male and 5 patients were female.

Table - 9 : Age group wise occurrence of PHN

S.No	*Age*	*Male*	*Female*	*Total*	*%*	*Associated Disease*
1.	10-20 years	0	1	1	5.2%	
2.	21-30 years	1	0	1	5.2%	HIV-I
3.	31-40 years	0	0	0		
4.	41-50 years	4	2	6	31.5%	Bronchial -1 Asthma
5.	51-60 years	3	0	3	15.7%	
6.	61-70 years	5	2	7	36.8%	Diabetes - 1
7.	71-80 years	0	0	0		
8.	81 & above	1	0	1	5.2%	
		14	5	19	100%	

The highest prevalence of PHN (36.8%) was noted in the age group of 61 to 70 years which was followed by 31.5% in the age group of 41 to 50 years and 15.7% in the age group of 51 to 60 years.

Minimum number of cases were observed in the groups of 10 to 20 years and 21 to 30 years of age with one case (5.2%) in each age group.

PHN was seen in a patient with HIV infection in one case, bronchial asthma 1 case and diabetes - 1 case.

Out of 19 cases of post herpetic neuralgia, 4 cases had spasmodic shooting pain, 2 cases had lancinating pain and the remaining 13 cases had burning type of pain.

Among the 19 cases of PHN, 12 cases were given T.Carbamazepine and 7 cases were given T. Amitriptyline.

DISCUSSION

Herpes zoster is common among immunocompromised persons, so the elderly are at particular risk because immunocompetence declines with age. Whitley et al[91] reported that zoster affects 20% of general population during their life time, especially in elderly. This study of hundred patients with herpes zoster revealed that the majority of the patients affected were adults in the second (25%), third (14%) and fourth (24%) decades. More than two thirds (73%) of the reported cases occurred in individuals below the age of 50 and the remaining 27% of affected cases were above 50 years of age. This is in contrast to the observation made earlier in other studies[25] where in more than two third of cases where in the age group above 50 years with highest incidence among individuals in the sixth to eighth decades of life.

Total number of cases in childhood and adolescence age group were ten (10) in number.

In this study male: female ratio was 2.5:1 which is in contrast with the Western Studies[92] where both male and female were equally affected.

Prodromal symptoms were in a higher rate (85%) in this study. In majority of cases dermatomal pain was the commonest prodromal symptom. This is in contrast to the lower incidence of prodromal symptoms (5%) observed in younger age groups, in various other studies[25].

In this study majority of the cases (74%) presented between 2 to 5 days and the remaining 26% of cases presented between 6 to 8 days and above, which is similar to the study report given in western literature[25].

Most common presenting symptom in this study was pain in 99% of cases and vesiculation was the next common presenting complaint in 98% of cases which is similar to various study reports[25,93].

Constitutional symptoms were noted in 75% of cases in this study and majority of cases were in younger age group.

This is in contrast to the lower incidence of prodromal symptoms (5%) observed, especially in younger age groups, in various other studies[25].

In this study 97% of cases had classical herpes zoster in dermatomal pattern[25] and 3% of cases had crusting and erosions. Thoracic dermatome was the most common dermatome involved

(60%) in this study followed by cervical dermatome in 9% of cases, ophthalmic zoster in 8% of cases and lumbar dermatome in 7% of cases, in accordance with the literature reports[33]. The least common dermatome involved was sacral segment.

Out of 100 cases 97% of cases had localised involvement with grouped vesicles and 1% of case had multidermatomal involvement, and the remaining 2% of cases had cutaneous dissemination in addition to the classical dermatomal distribution. Multidermatomal and disseminated zoster was more frequent in males than females Multidermational zoster case with Ramsay Hunt syndrome was reported with malignancy.

One case of disseminated zoster was associated with HIV infection. Lymph node enlargement was noted in 95% of cases.

Thirty six cases were having one or more suspected provocative factors. Out of 36 cases most common risk factor seen was HIV infection in 16 cases (44.4%) followed by diabetes in 7 cases (19.4%) and 5 cases (13.8%) on steroid therapy. Malignancy, radiotherapy, Hansen's disease, tuberculosis, renal transplantation, physical stress of parturition and pregnancy were also noted as provocative factors one case each. Depressed cell medicated immunity associated with the above conditions, as described in literature[25] could be the possible factors for the development of zoster.

Past history of chicken pox was given by 90% of cases. The remaining 10% of cases were either not aware of or not had chicken pox.

Systemic diseases seen in association with herpes zoster were diabetes mellitus 7 cases, hypertension 6 cases, SLE 3 cases, bronchial asthma 2 cases, tuberculosis 1 case, hepatitis B infection 1 case and chronic renal failure 1 case.

Few cutaneous diseases seen in herpes zoster patients in this study and those cases were acne (1 case), tinea versicolor (2 cases), seborrheic dermatitis (2 cases), SLE (3 cases), insect bite allergy (2 cases) and Hansen's disease, cellulitis, oral candidiosis, tinea cruris and intertrigo, one case each.

Most of these cases were associated with immunosuppression.

Period of time taken for resolution or healing of the lesions, in this study, ranged from 2 to 4 weeks, as described in literature[33].

Tzanck smear was positive in 95% of cases with vesicular lesions and it was negative in 5% of cases with erosions, crusting and ulceration correlates well with that of literature reports[25]. Complete hemogram was normal in 68% of cases in this study. This is in contrast to the literature reports, where in normal complete hemogram results are reported in zoster patients[93]. Raised ESR was

noted in 20 patients, increased eosinophil and neutrophil count noted in 6 patients each and decreased hemoglobin value was noted in 4 patients.

Blood sugar was elevated in above normal value in 7 patients. Urine routine examination was normal in almost all patients (98%). Urine examination showed reducing sugar in 2 patients (2%).

In this study, 16% cases of the 100 patients who were tested for HIV were sero positive. Among the 16% of cases of HIV positivity, herpes zoster was the presenting disease for HIV infection in 6% cases, and 10% cases developed herpes zoster during the course of HIV infection. Results of this study showed higher incidence of herpes zoster in HIV infection. Recurrence of zoster lesions in HIV positive patients were not observed in this study.

Skin biopsy showed histopathological features as described in literature[25, 11].

ECG was taken for all cases with lesions involving left upper thoracic dermatomes and no abnormality was detected.

Post herpetic neuralgia was the commonest complication noted in 19 patients (47.5%) followed by secondary bacterial infection in 15 cases (37.5%), scarring in 5 cases (12.5%) and motor

zoster (facial palsy) in 1 case (2.5%). Post herpetic neuralgia is the commonest complication reported in the literature[33].

In accordance to the literature reports[33], the incidence of post herpetic neuralgia increased with increasing age in this study.

CONCLUSION

1. In this study herpes zoster mainly occurred in second, third and fourth decades of life. More than two third (73%) of cases occurred in individuals below the age of 50 years.

2. Male preponderance in incidence was found with the sex ratio of 2.5:1

3. Prodromal symptoms were present in 85% of patients and dermatomal pain was the commonest prodromal symptom.

4. Most common presenting symptom was pain in 99% of cases, followed by vesiculation in 98% of cases.

5. Constitutional symptoms were noted in 75% of cases and majority of cases were in younger age group.

6. Thoracic dermatome was the most common dermatome involved and sacral segment was the least common dermatome affected.

7. HIV infection was present in 16% of total cases. Out of this, 10% of cases were already diagnosed as HIV

positive and developed herpes zoster during the course of HIV disease and herpes zoster was the presenting disease of HIV infection in 6% of cases. This indicates the importance of HIV testing in all patients presenting with herpes zoster, especially in patients below the age of 50 years.

8. No significant association of herpes zoster was found with any other skin disorder in this study.

9. The most common systemic diseases noted were diabetes mellitus, hypertension and are considered coincidental. Other systemic diseases associated with herpes zoster were SLE bronchial asthma, tuberculosis, chronic renal failure and hepatitis B infection. Steroid therapy given for certain systemic disorders and decreased CMI acted as provocative factor for herpes zoster.

10. Duration of time taken for resolution or healing of the lesions, ranged from 2 to 4 weeks.

11. Post herpetic neuralgia was the commonest complication (47.5%) and the incidence of PHN increased with increasing age. The other complications

noted were secondary bacterial infection, scarring and motor zoster (facial palsy).

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PROFORMA

Name : Age : Sex :

Hospital No. : Case No.

Occupation : Address :

PRESENTING COMPLAINTS:

H/O. PRESENT ILLNESS

H/o. vesicles - onset, progression, duration

H/o. Pain and nature of pain

H/o. Paraesthesia

H/o. Fever, Malaise

H/o. Itching, tingling, numbness over the involved site

H/o. Difficulty in swallowing

H/o. Pain & Photophobia in eye

H/o. Watering in eye

H/o. Headache

H/o. Toothache (Oro facial Zoster)

H/o. Otalgia

H/o. Tinnitus and giddiness

H/o. Difficulty in urination / defecation

H/o. Treatment

H/o. Diabetes

H/o. Malignancy

PAST HISTORY

H/o. Varicella

H/o. Diabetes, TB

H/o. Recurrent Zoster

TREATMENT HISTORY

H/o. Treatment for malignancy

H/o. Steroid therapy / Other immunosuppressive drug therapy

H/o. Treatment for HIV

H/o. Treatment for Diabetes

H/o. Radiotherapy

FAMILY HISTORY

H/o. Varicella in any other family members (for contact exacerbation)

PERSONAL HISTORY

H/o. Alcoholism / Smoking

H/o. Sexual exposure

MENSTRUAL HISTORY

GENERAL EXAMINATION

Anemia, Jaundice, Edema, Lymphadenopathy (Regional / Generalised)

SYSTEMIC EXAMINATION

CVS : RS:
Abd : CNS:

DERMATOLOGICAL EXAMINATION

SKIN

- Site of Lesion Dermatome involved
- Distribution of Vesicles Grouped or Scattered
- Stages of Vesicles Erythema, Papules, Vesicles, Crust
- Hyperaesthesia
- Complications:
  Secondary infection, Ulceration, Post inflammatory hypo/hyper pigmentation, Scarring
- Mucosa
- Hair and Nail
- Palms and Soles

INVESTIGATIONS:

Blood	-	TC, DC, ESR, Hb%
Blood	-	Sugar
		Urea
Serum	-	Creatinine
Urine	-	Albumin
		Sugar
		Deposit
Tzanck Smear	-	
ECG (When it is needed)	-	
ELISA	-	
Specialist opinion (for selected cases)		
Biopsy (If necessary)	-	

TREATMENT

T. Aciclovir as per the requirement

Other supportive measures

FOLLOW UP: (For 3 Months)

- PHN
- Other Complications

ACRONYMS

Sl. No.	*Acronyms*	*Expansion*
1.	PHN	Post Herpetic Neuralgia
2.	HIV	Human Immuno Deficiency Virus Infection
3.	N	Normal
4.	POS	Positive
5.	Neg	Negative
6.	Zinc Cal Lotion	Zinc Oxide Calmine Lotion
7.	ACV	Aciclovir
8.	SSD	Silver Sulphadiazine Cream
9.	Carbamaz	Carbamazepine
10.	ESR	Erythrocyte Sedimentation Rate
11.	ELISA	Enzyme Linked Immuno Sorbent Assay
12.	Bd	Blood
13.	RFT	Renal Function Test
14.	ECG	Electro Cardiogram
15.	CRF	Chronic Renal Failure
16.	ART	Anti Retroviral Therapy
17.	HT	Hypertension
18.	SLE	Systemic Lupus Erythematosus
19.	Hb	Haemoglobin
20.	Seb Derm	Seborrheic Dermatitis
21.	IBA	Insect Bite Allergy
22.	TB	Tuberculosis
23.	ATT	Anti Tuberculosis Therapy

Sl. No.	***Acronyms***	***Expansion***
24.	BL	Borderline Lepromatous Leprosy
25.	LL	Lepromatous Leprosy
26.	MB - MDT	Multi bacillary - Multi Drug Therapy
27.	ANC	Antenatal Case
28.	HBV	Hepatitis B Virus Infection
29.	RT	Radiotherapy
30.	Ca Cx	Carcinoma Cervix
31.	Rt	Right
32.	Lt	Left
33.	TV	Tinea Versicolor
34.	VZV	Varicella Zoster Virus