Ministry of High Education and Scientific Research
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Post-herpetic neuralgia

A Project Submitted to the College of Dentistry, University of Baghdad, Department of Oral Diagnosis /Oral Medicine Clinic in Partial Fulfillment of the Requirement for B.D.S.

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فَتَعَالَى اللَّهُ الْمَلِكُ الْحَقُّ ۗ وَلَا تَعْجَلْ بِالْقُرْآنِ مِنْ قَبْلِ أَنْ يُقْضَىٰ إِلَيْكَ وَحْيُهُ ۖ وَقُلْ رَبِّ زِدْنِي عِلْمًا ﴿١١٤﴾ سورة طه

Dedication

To the one whom I could not comprehend, so he improved my manners and created me, then provided me with sustenance

So he completed his generosity with the most generous generosity and to everyone who sought and is still striving in my success and excellence.

And to those eyes that enchanted me, inspiring me patience and strength

And to the one who bestowed upon me the best of knowledge

Acknowledgment

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ABSTRACT

Post-herpetic neuralgia (PHN) is a chronic neuropathic pain condition that persists 3 months or more following an outbreak of shingles. Shingles, also known as acute herpes zoster, is associated with the reactivation of the dormant varicella zoster virus in an individual who has experienced chicken pox. PHN is associated with persistent and often refractory neuropathic pain. Patients may experience multiple types of pain including a constant deep, aching, or burning pain; a paroxysmal, lancinating pain; hyperalgesia (painful stimuli are more painful than expected); and allodynia (pain .(associated with typically non-painful stimuli

Etiology of Post _herpetic neuralgia approximately 10% if patients who have suffered recurrent VZV infection.

Epidemiological studies of Post herpetic neuralgia, prevalences and incidences.

Risk factors of PHN including age, sex, immunosuppression, cancer and others.

Signs and symptoms of PHN are sharp , burning, jagging ,aching pain in the area of affected site

in rare cases also controls muscle movement.

Complications of post herpetic neuralgia can cause tiredness, trouble sleeping and also depression from long period of pain .

Diagnosis in this research by many methods and the most important one is history of herpes virus.

Prevention and treatment of post herpetic neuralgia are therapy and possibly low-dose tricyclic antidepressants to prevent post herpetic neuralgia. There is good evidence that treating herpes zoster with antiviral medication is beneficial, particularly in patients older than 50 years with severe outbreaks. The pharmacological treatment of PHN may include a variety of medications including alpha-2 delta ligands (gabapentin and pregabalin), other anticonvulsants (carbamazepine), tricyclic antidepressants (amitriptyline, nortriptyline, doxepin), topical analgesics (5 % lidocaine patch, capsaicin) tramadol, or other opioids.

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PHN	Post-herpetic neuralgia
VZV	Varicella-zoster virus
HZ	Herpes zoster
FU	Fluorouracil

NSAID	Non-steroidal anti-inflammatory
TPRV1	Transient receptor potential vanilloid 1
TCAs	Tricyclic antidepressants
SNRIs	Serotonin norepinephrine reuptake inhibitors
ESI	Epidural steroid injection
DREZ	Dorsal root entry zone

Introduction

Post-herpetic neuralgia (PHN) is the most common long-term complication of varicella-zoster virus (VZV) reactivation , This reactivation of the dormant VZV is known as herpes zoster or shingles, VZV is the pathogen that causes the once common childhood condition varicella, colloquially known as chickenpox.[1,2]

Etiology of (PHN) approximately 10% of patients who have suffered recurrent VZV infection of the trigeminal nerve (shingles, herpes zoster) subsequently develop persistent neuralgia, Damage to neural tissue or the persistence of VZV within the trigeminal nerve has been implicated in this condition.[3]

Epidemiological of PHN the specific incidence of PHN in the trigeminal region is not known; however, the overall PHN incidence is estimated at 3.9-42/100,000 person per year.[4]

The frequency of persistent pain 3months following acute herpes zoster increase with age, ranging from 0.3% in patients under 44 years old 9% in those 75 and older, that observed in the female more than male.[5]

Several risk factors for the development of PHN in HZ patients have been cited, including age, sex, clinical characteristics of the HZ episode, chronic morbidities, immunosuppression, cancer and others. Among these, older age is the most certain and widely recognized risk factor, while the role of sex seems to be controversial.[6]

Sign and symptoms of (PHN) the hallmark of PHN is a lancinating/burning pain in a unilateral dermatomal pattern that persisted for three or more months after the onset of a herpes zoster (HZ) outbreak.[7]

The affected areas are usually hypo esthetics or anesthetic with pale or red/purple scar, these anesthetic scars often exhibit allodynia and hyperplasia, no different from other neuropathic pain conditions, a heterogeneous mix of sensory sign and symptoms are observed in PHN.[8]

The complications of post herpetic neuralgia are **:**

-Tiredness

-(Trouble sleeping) (insomnia)

-Decreased appetite

-Poor concentration

-Pain from long-lasting PHN can lead to depression.[9]

Treatment of (PHN) the most successful treatments are multi-modal, with some researchers/clinicians focusing on prevention in high-risk populations rather than cure because of the debilitating and often refractory nature of PHN in already fragile patient populations.[10]

Three fundamental treatment approaches may be considered for PHN.[10]

The first is prevention, which focuses on identifying populations at risk for contracting HZ and administering a vaccine. The second is early recognition and treatment of an acute HZ infection, as delay may increase the chance of developing PHN. The third approach is symptom management of PHN via multimodal medication regimens and interventional procedures.[11]

Review of Literature

1.1-Herpes Zoster(HZ)

1.1.1-Definition

Herpes zoster(HZ) is a clinical manifestation of the reactivation of latent varicella zoster virus infection, it is a cause of considerable morbidity, especially in elderly patients, and can be fatal in immunosuppressed or critically ill patients, the pain associated with herpes zoster can be debilitating, with a serious impact on quality of life, and the economic costs of managing the disease represent an important burden on both health services and society, here we provide an overview of the disease and a summary of “best practice guidance” for the management of herpes zoster and its sequelae, detection of VZV DNA in cerebrospinal fluid,

for localized zoster transmission occurs through contact with the fluid in the blisters of the rash. A person is not infectious before the blisters appear or after the rash has crusted over,

for disseminated zoster, transmission occurs through airborne and droplet transmission, in addition to contact with fluid in the blisters of the rash. Disseminated zoster is likely as infectious as varicella. [12]

Herpes zoster, or shingles, is the painful eruption of a rash, usually unilateral, caused by the varicella zoster virus, varicella zoster virus usually persists asymptomatically in the dorsal root ganglia of anyone who has had chickenpox, reactivating from its dormant state in about 25% of people to travel along the sensory nerve fibers and cause vesicular lesions in the dermatome supplied by that nerve ,herpes zoster is more common in people with diminished cell mediated immunity, this includes elderly people, patients with lymphoma, those receiving chemotherapy or steroids, and people with HIV, in Contrast to herpes simplex, precise triggers for herpes zoster are not known.[13]

1.1.2- Etiology and Pathophysiology

Peripherally, viral replication induces epithelial cell degeneration and ballooning, followed by invasion of giant cell, in rare cases, necrosis and bleeding are observed, the vesicles rupture and release infectious contents, activation of varicella zoster virus at the spinal root or cranial nerve neurons results in an inflammatory response that may also include the leptomeninges, nerve damage following inflammation around the nerve trunk with lymphocytic infiltration of the nerve root contributes to pain in HZ, the ongoing inflammation may induce neuronal loss, fibrosis, and focal necrosis of nerve cells and satellite cell bodies, infected DRG cells demonstrate cell degeneration and accumulation of glia cells, the distribution of sensory changes and development of hyperalgesia are associated with the spread within the spinal cord.[14]

1.1.3- Epidemiology

Herpes Zoster does not generally have epidemics and does not follow a seasonal pattern, the annual incidence has been reduced significantly since the introduction of the first varicella vaccination in 1995, HZ incidence increases with age, approximately 0.3% of the population will develop HZ, more than 50% of patients over the age of 80 are at risk to develop HZ, and the overall lifetime risk to develop HZ is estimated as 30%, HZ is not common among young patients, and it remains to be determined when the presence of HZ in young patients should be interpreted as a sign of underlying immunosuppressive disease.[15]

1.1.4-Clinical Features of Acute Herpes Zoster

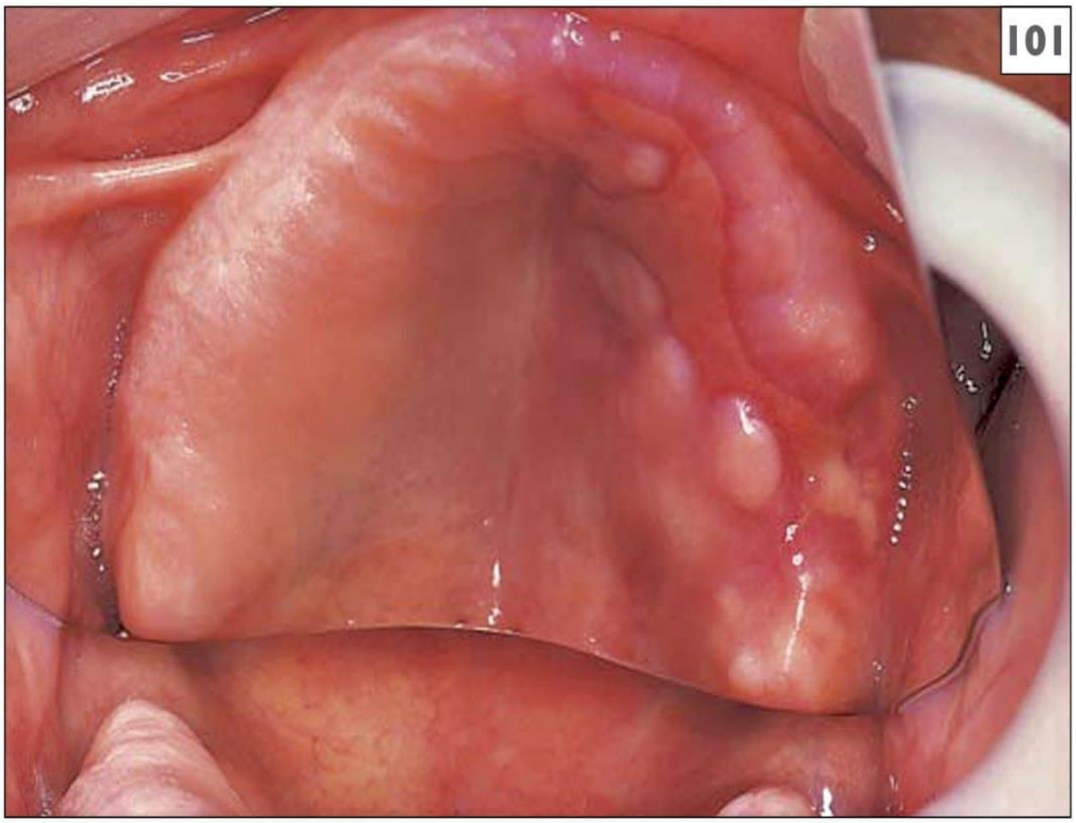
Acute HZ is characterized by a unilateral, dermatomal, red maculopapular rash that matures into vesicular eruptions over 3-5 days, the vesicles dry within another 7-10 days, complete healing may take a month, HZ virus most commonly affects the thoracic nerves, followed by the lumbar region, the trigeminal affected in 8-28% of cases, among the trigeminal cases, the ophthalmic branch involvement is most common, occurring in 80% of cases.[16]

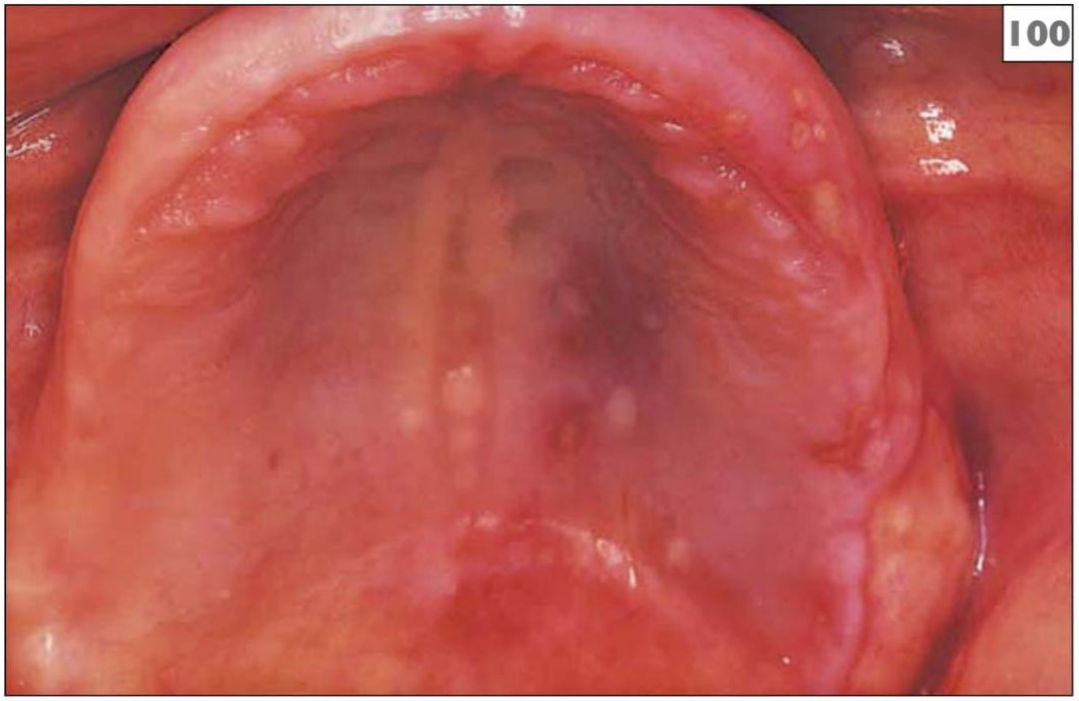
Ophthalmic nerve involvement can result in keratitis, a vision-threatening condition, when the maxillary or mandibular branches are affected, the vesicles may appear intraorally, cervical nerves are affected in 13-23% of cases, pain in HZ is constant with superimposed piercing attacks, evoked pain may be the prominent feature in some patients, the pain quality varies: burning (26%), stabbing (15%), shooting (15%), tingling (10%), and aching (9%) common descriptors used, its intensity is moderate to severe (VAS 6.2 average), but up to 25% of patients have no pain, high pain severity correlates with an increased incidence of Post Herpetic Neuralgia (PHN)," In three-quarters of the patients, acute HZ presents with prodromal pain, headache, itching, malaise, and fever, the develops 2-3 days (< 7) prior to acute HZ and may last with varying intensity up to 3-6 months after healing, acute HZ patients may have mechanical allodynia and altered sensory thresholds that can spread to adjacent dermatomes, but is rarely bilaterally, motor weakness may occur, but is usually transient, dermatomal pain with no rash, termed "zoster sine herpete," is very rare and its diagnosis requires evidence of con-current viral reactivation.[17]

1.1.5- Diagnosis

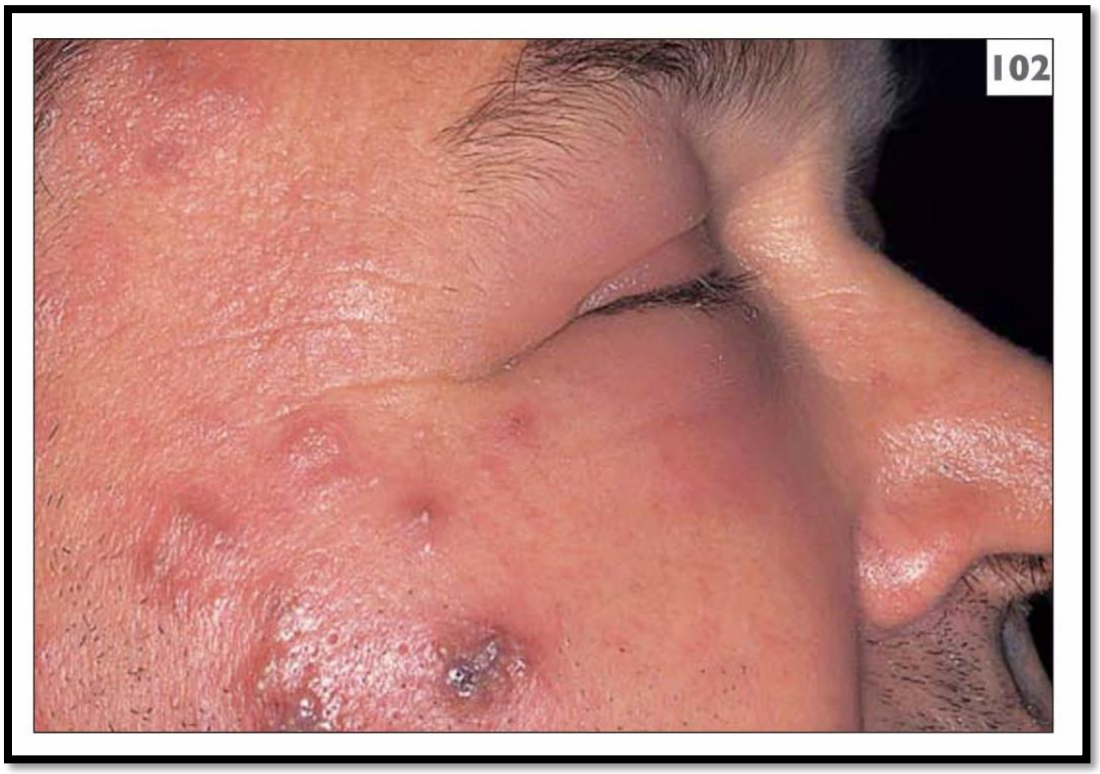
Herpes zoster can usually be diagnosed clinically, however, early zoster and zoster presenting in the sacral and cervical area may be difficult to distinguish from herpes simplex, in these cases, the diagnosis can be confirmed by sending swabs to the local virology laboratory, but treatment should not be delayed while waiting for test results, the top of the lesion should be lifted and a sterile swab used to rub base of the lesion, the swab should then be wiped across a sterile glass side or over three wells on a Teflon coated slide, the slide should be air dried and sent to the laboratory for staining with immuno-fluorescent antibodies, the swab can also be placed in viral transport medium or sterile saline, which is suitable for transporting to the laboratory within the next one to three days for detection of viral DNA by polymerase chain reaction, reactivation of varicella zoster virus in immuno-compromised patients, especially those who have had bone marrow or solid organ transplants,

may spread to involve the gut, liver, and other viscera, although atypical rash is common, some cases present with abdominal pain and no evidence of rash, in the absence of rash, the diagnosis can be confirmed by measuring virus in the blood by polymerase chain reaction.[18]





Figure(1-1) Unilateral lesions of recurrent varicella zoster virus infection[18]



Figure(1-2) Vesicular eruption of herpes zoster on the skin.

1.1.6-Complications of Herpes Zoster.

These occur in a minority of patients and are more frequent in older or immunosuppressed patients,

Post herpetic neuralgia

Post herpetic neuralgia is considered the most common .[1] complication and increases with age, affecting up to 30% of people with herpes zoster over the age of 80 years, it is generally defined as pain of at least moderate intensity persisting for three months or longer, although various definitions (and measures of pain severity) have been used in drug trials.[19] It may occasionally last for years, post herpetic neuralgia is characterized by constant or intermittent, usually severe, burning or lancinating pain that occurs almost daily, allodynia is present in most cases and can make even wearing clothing an arduous task, quality of life is invariably reduced, features that appear to be predictive for the development of post herpetic neuralgia include more severe initial pain, more extensive rash and age over 50 year.[19]

Table(1-1)(Risk factor for development of post herpetic neuralgia).[20]

Box 1 | Risk factors for development of postherpetic neuralgia after an attack of herpes zoster

- Advanced age (›50 years)
- Female sex
- Presence of a prodrome
- Severe or disseminated rash
- Severe pain at presentation (visual analogue score ›5)
- Polymerase chain reaction detectable varicella zoster virus viraemia

Ocular involvement

Herpes zoster ophthalmicus occurs in 10–25% of cases, this involves the ophthalmic branch of the trigeminal nerve and results in a disproportionately high complication rate (50% in the absence of antiviral drugs) with the eye affected in several possibleways.[21]

Keratitis occurs in about two-thirds of cases and conjunctivitis, uveitis, retinitis and glaucoma can all occur, the presence of vesicles on the nose (Hutchinson's sign) due to involvement of the nasociliary branch of the trigeminal nerve has been found to be highly predictive of eye involvement.[23]

Table(1-2) complication of herpes zoster ophthalmicus.[20]

Box 2 | Complications of herpes zoster ophthalmicus

- Conjunctivitis, episcleritis, and scleritis
- Keratitis, iridocyclitis
- Choroiditis, papillitis
- Oculomotor palsy
- Retinitis
- Optic atrophy

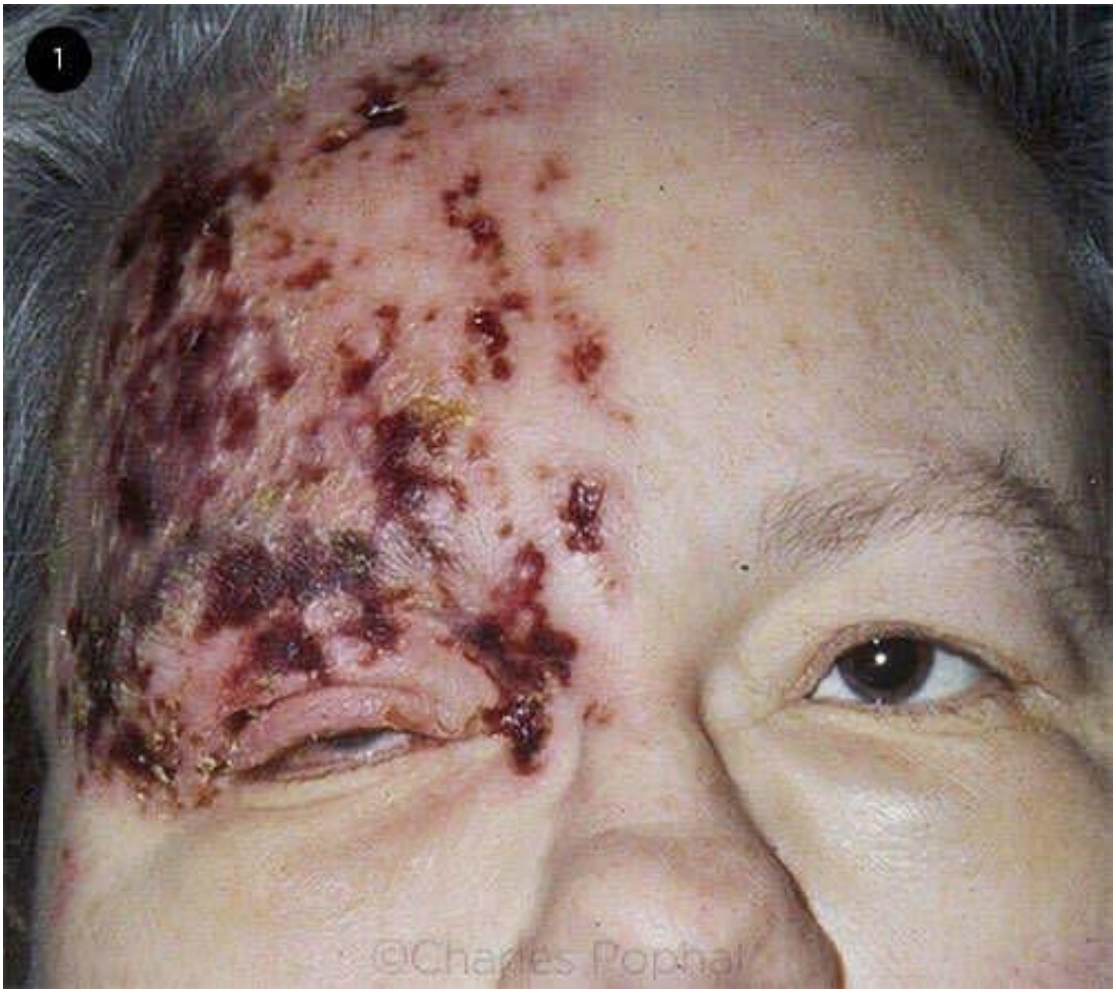
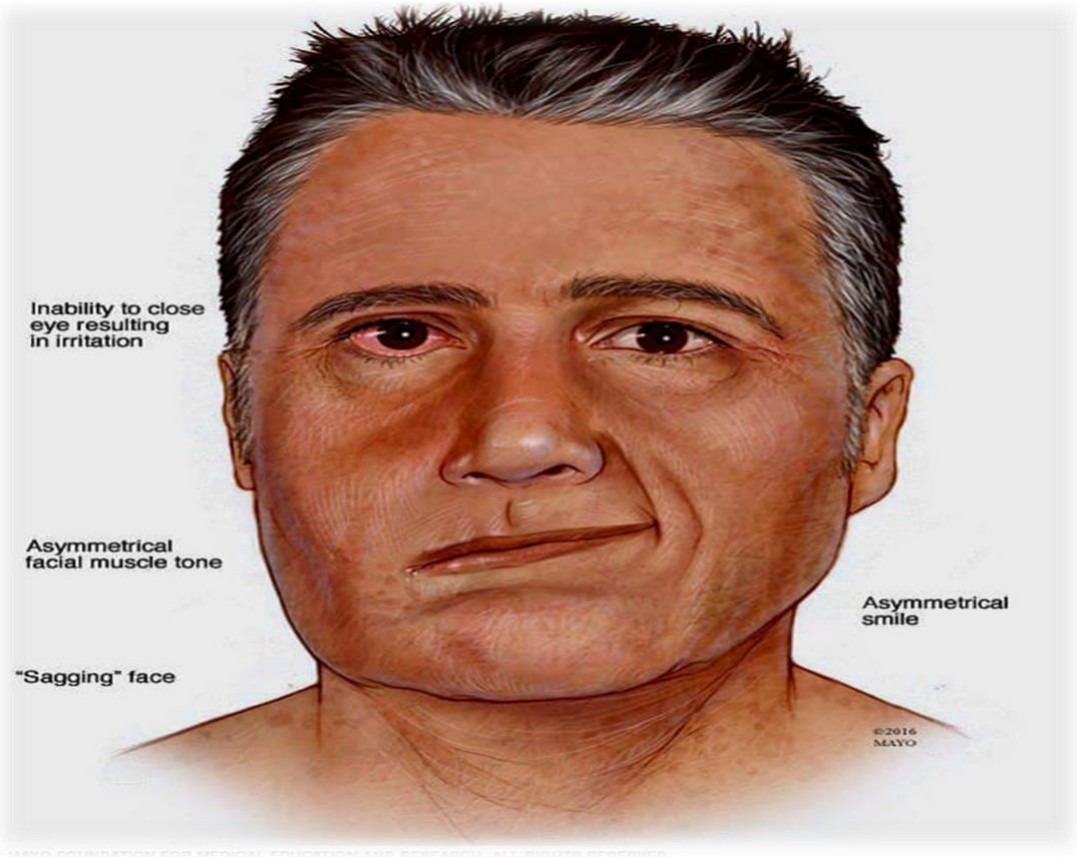


Figure (1-3) Herpes Zoster Ophthalmicus.[23]

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, rarely, aseptic meningitis, myelitis, peripheral motor neuropathy, cerebellar syndromes, and stroke syndromes due to involvement of cerebral arteries (varicella zoster virus vasculopathy) can occur.[22]



Figure(1-4) Ramsay Hunt Syndrome.[21]

Disseminated zoster

Most individuals with herpes zoster will have some lesions outside the primary dermatome. Disseminated zoster is defined as 20 lesions or more outside the involved dermatome, it tends to occur only in immunocompromised patients and may be associated with visceral involvement (lungs, liver, gut and brain).[21]

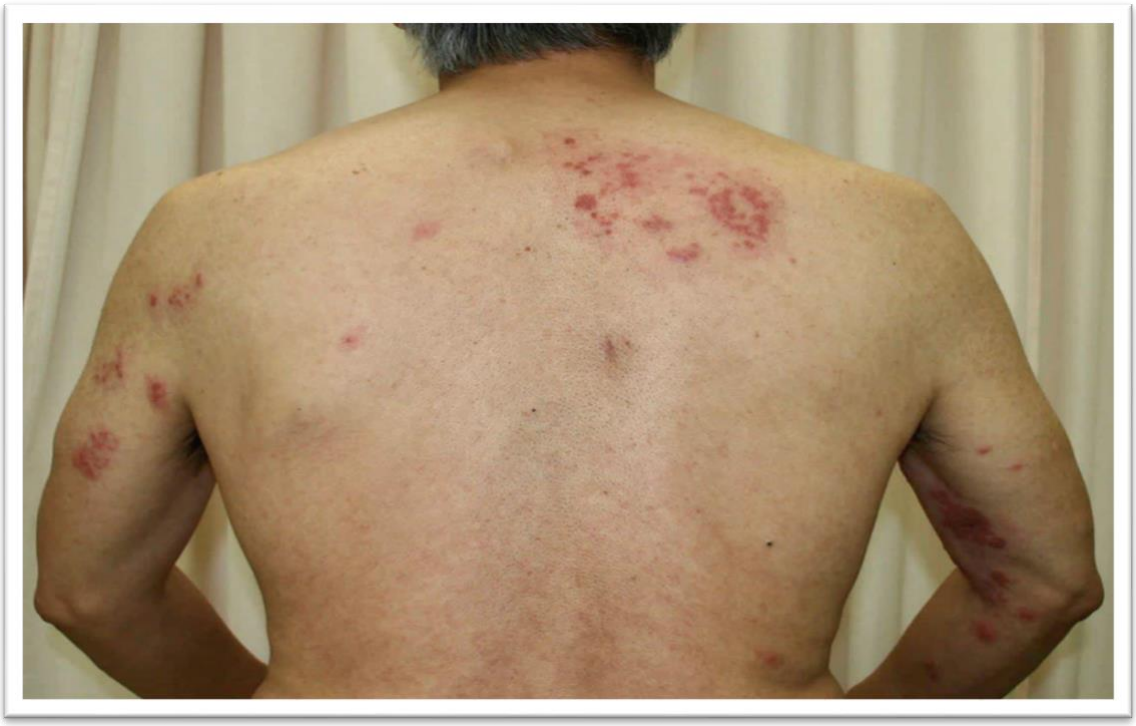


Figure (1-5) Disseminated Herpes Zoster.[21]

Bacterial infections

If bacterial super infection is suspected, antibiotic treatment to cover Staphylococcus aureus and Streptococcus pyogenes should be considered, for example di/flucloxacillin 500 mg every six hours for seven days.[20]

1.1.7- Management of Herpes Zoster

Acute HZ treatment is focused on pain control, reducing the risk of complications such as spreading and local secondary infection, post herpetic neuralgia (PHN), as well as efforts to accelerate healing.[23] Early initiation of antiviral treatment (less than 72 hours following rash onset), mainly in patients older than 50 years, shortens the rash duration and reduces pain severity and frequency. [23,24] Meta-analyses, however, did not find significant reductions in PHN incidence following , oral acyclovir therapy.[23]

Antiviral Medications

The antiviral medications used to treat acute HZ include valacyclovir (1000 mg x 3/d), acyclovir (800 mg x 5/d), and famciclovir (500 mg x 3/day). Valacyclovir is more efficacious than acyclovir in terms of pain resolution, famciclovir is well-tolerated therapy that 17 has the advantage of reduced frequency of dosing. [25]Brivudin is an antiviral medication that is available in some countries for the early treatment of HZ, mainly in immunocompetent adults, overall, brivudin (125 mg daily) is superior to acyclovir (800 mg x 5/d), however it has a mixed efficacy profile. [23] Brivudin and famciclovir (250 mg x 3/d) are comparable in effectiveness on pain and rash with similar tolerability. Severe drug interactions have been reported between brivudin and 5-fluorouracil (FU) and other 5-fluoropyrimidines; therefore, brivudin should not be used along with 5-FU or its derivatives, capecitabine, floxuridine, or flucytosine, newer anti-HZ drugs, such as the bicyclic nucleoside analogue FV-100, the helicase-primase inhibitor ASP2151, and valomaciclovir, have been evaluated in clinical trials and offer promising improved efficacy, reduced daily doses, and side effects.[26]

Systemic administration of corticosteroids in combination with antiviral medication offers clinically significant benefits for acute pain and quality of life outcomes when administered systemically within 72 hours of rash onset.[27]

Pain medications

Analgesics such as paracetamol or non-steroidal anti-inflammatory drugs (NSAIDs) should be used to control fever and pain, stronger pain may require analgesic/NSAID combinations or short-term opioid treatment, mainly for nonresponsive pain, amitriptyline and gabapentin are centrally acting analgesics that can also provide some pain relief, amitriptyline may be associated with cardiovascular effects, which limit its use in the elderly and medically complex patients.[28]

Table(1-3) Treatment of acute herpes zoster in immunocompetent adults.[20]

Table 1 | Treatment of acute herpes zoster in immunocompetent adults

Drug	Dose/frequency	Treatment duration	Efficacy	Notes
Aciclovir	800 mg five times daily*	7-10 days	Reduces acute pain and development of PHN	Most effective if started within 72 hours of onset of rash
Famciclovir	750 mg daily* or 250 mg three times daily	7 days	Reduces acute pain and development of PHN	Most effective if started within 72 hours of onset of rash
Valaciclovir	1 g three times daily*	7 days	Reduces acute pain and development of PHN	Most effective if started within 72 hours of onset of rash
Brivudin	125 mg daily	7 days	Reduces acute pain and development of PHN	Licensed for treatment in Austria, Belgium, Germany, Greece, Italy, Luxembourg, and Spain
Prednisolone	60 mg daily initially, then taper dose	21 days	Reduces acute pain	Use only in combination with antivirals. Reduce dose to 30 mg after 7 days and to 15 mg after a further 7 days, then stop
Amitriptyline	25 mg daily	3 months	Reduces incidence of PHN; effect on acute pain uncertain	Use with care in elderly patients. An electrocardiogram should be done before treatment

PHN=postherpetic neuralgia.

Review of literature

1.2-post-herpetic neuralgia(PHN)

1.2.1-Definition

Post herpetic neuralgia (PHN) is a neuropathic pain syndrome characterized by pain that persists for months to years after resolution of the herpes zoster (HZ) rash.[31-32] HZ, also known as shingles, is a distinctive clinical condition caused by the reactivation of varicella zoster virus (VZV), which starts residing latently in the body after a primary varicella (chickenpox) infection, which may have occurred decades earlier.[31-33]

Reactivation of VZV can also produce chronic neuropathic pain without rash (zoster sine herpete), which can be more challenging to diagnose and may involve testing the cerebrospinal fluid.[34-35]

PHN is preceded by the characteristic neuropathic dermatomal pain and rash (Figure1-6), although there have been instances of PHN without this prodrome (as in zoster sine herpete, where diagnosis is confirmed with serologic studies).[36-37]

Figure(1-6) Varicella zoster virus reactivation ;shingles presentation.[36-37]

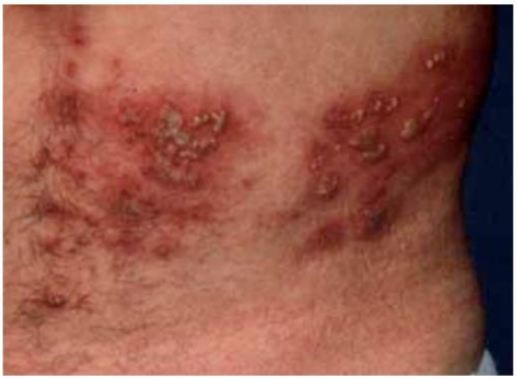


Figure Varicella zoster virus reactivation: shingles presentation.

A commonly used definition of delineating PHN is suggested by Dworkin as a "significant pain or abnormal sensation 120 days or more after the presence of the initial rash," It generally affects the thoracic derma tomes, although cervical and thoracic dermatomes also may be affected; however, in 23% of the cases, the ophthalmic division of the trigeminal nerve is affected.[39-40]

1.2.2-clinical presentation and Pathophysiology

VZV is a highly contagious DNA virus that remains latent within the sensory ganglia following resolution of chickenpox, which usually occurs during childhood.[33] During HZ, VZV is reactivated, travels back along the affected neurons away from the sensory ganglia, and propagates in the epidermis, a hallmark of HZ is that it is typically unilateral (ie, not

crossing the midline), and in most cases only a single dermatome is affected, the erythematous maculopapular HZ rash is usually accompanied by pain and dysesthesia, the rash progresses to clear vesicles similar to the original chickenpox outbreak, then, over a period of 48–72 hours, pustules form, ulcerate, and eventually scab over, scabs fall off in 2–3 weeks and scarring may occur.[41]

PHN occurs in the same dermatomes as the HZ rash, and stems from damage to peripheral and central neurons that may be a byproduct of the immune/inflammatory response that accompanied VZV reactivation and migration.[33-42] When damaged, peripheral and central nerve fibers may develop a lower threshold for action potentials, discharge spontaneously, and exhibit disproportionate responses to stimuli, resulting in peripheral sensitization and pain without painful stimuli (allodynia).[33-42]

Patients with PHN experience three major types of pain:

1) constant pain without a stimulus (often described as burning, aching, or throbbing),

2) intermittent pain without a stimulus (often described as stabbing, shooting, or electric shock-like),

and 3) pain brought on by a stimulus but is disproportionate to the stimulus (hyperalgesia), enduring for at least 3 months after healing of the HZ-related skin rash.[32-33]

In addition, patients may experience a variety of abnormal sensations (dysesthesias or paresthesias), patients with PHN report decreased quality of life and interference with activities of daily living that may affect physical, psychological, and social aspects of their lives as well as their ability to function.[43]

The pathophysiology behind PHN is a neuronal injury that affects both the peripheral and central components of the nervous system (Figures1-7) , this injury causes peripheral neurons to generate spontaneous discharges, while also lowering the threshold for action potentials that generate disproportionate pain, often with non-painful stimuli.[43-44] Skin biopsies taken in studies of patients with PHN showed severe loss of epidermal free nerve endings in the affected area. [39-45] However, reinervation is not required for pain resolution.[45-33]

At a cellular level, evidence shows an increase in the number of voltage-gated sodium channels.[46] Potassium voltage-gated channel alterations, and up-regulation of receptors associated with pain such as transient receptor potential vanilloid 1 (TPRV1).[47] These changes are associated with spontaneous and provoked pain due to a lowered threshold for action potentials, TPRV1 has been studied as a nonselective calcium channel with high calcium permeability that is expressed at the terminal endings of peripheral small-diameter sensory neurons, thus, inhibition of the TPRV1 receptor may prevent the action potential at the peripheral neurons that lead to pain transmission.[48] There also is evidence of loss of GABAergic inhibitory interneurons at the dorsal horn, as well as loss of descending inhibition.[47]

In addition to sensory neuron damage, motor deficiency can occur from inflammation affecting the anterior horn of the spinal cord.[49-50]

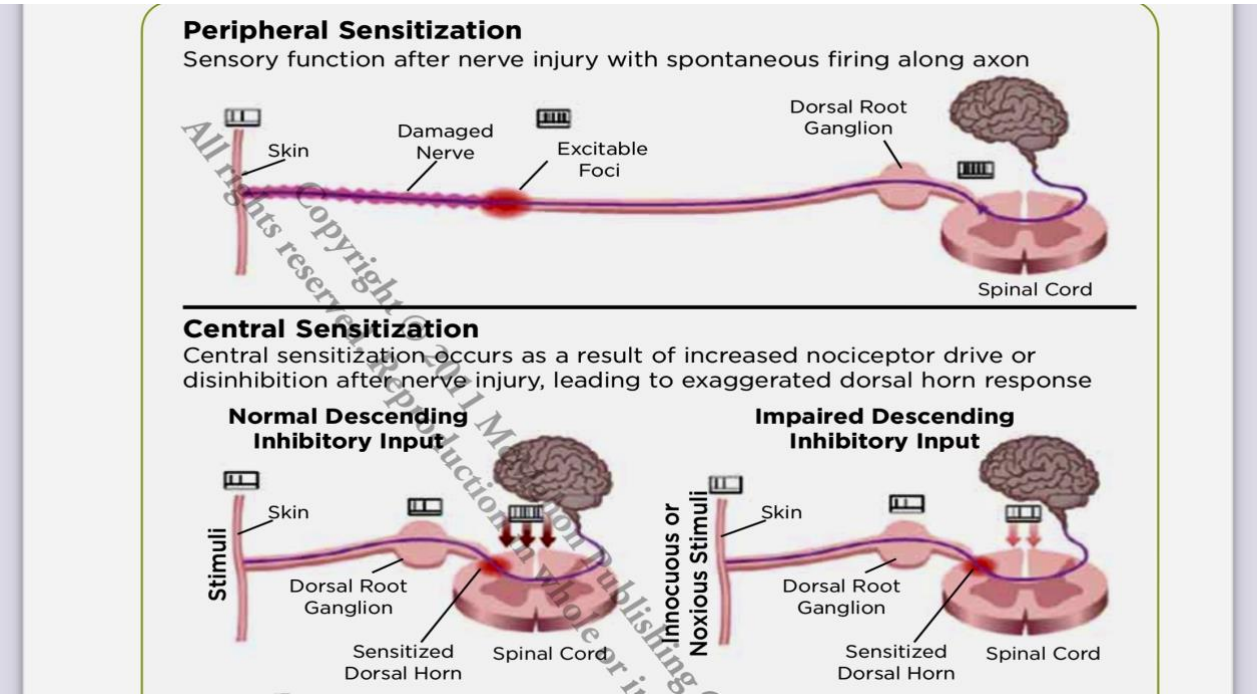
PHN has further been divided into 2 clinical patterns: irritable nociceptor and deafferentation.[51] Irritable nociceptor presents itself as severe allodynia with minimal if any sensory loss, which correlates with C-fiber activity, C-nociceptors normally are only stimulated by noxious stimuli; however, with the phenotypic changes described above (such as that seen in PHN), they become sensitized, lower their threshold for activation, and increase their discharge magnitude,

the clinical outcome is peripheral nervous system-mediated allodynia,

Deafferentation is associated with sensory loss and allodynia at the area of scarring, the deafferentation results in dorsal horn reorganization, the sensitized C fibers that are associated with the peripheral pain diminish in quantity with deafferentation, this leads to sprouting of AB fibers (large-diameter fibers that respond to mechanical stimuli such as touch and pressure) that ultimately causes them to make connections with the spinothalamic tracts of the spinal cord that are normally synapsing with the C fibers to trans mitpain. [51]

The clinical outcome of this reorganization due to C-fiber degeneration and resultant rewiring is that touch and pressure types of peripheral stimuli now cross-talk with pain-transmitting spinothalamic tracts in the

spinal cord, producing allodynia mediated by the central nervous system, central sensitization also plays a prominent role in PHN because the insulting injury leads to an overall augmentation in the excitability of the spinal cord neuron, which in general suggests that any input from nociceptors will generate an enhanced response. [51]



Figure(1-7) Examples of peripheral versus central sensitization.[43-44]

1.2.3-Epidemiology

Risk factors for developing PHN after a herpes zoster infection include older age, immunosuppression, female gender, greater acute pain and dermatomal injury, and severe prodrome.[41-52-53-54]

An incidence of greater than 20% is associated with those over age 50 and approximately a 35% risk in those over 80, whereas there is only about a 2% risk in those under the age of 50.[55]

Elderly individuals tend to have greater dermatomal eruptions and nerve damage that can be associated with their decreasing cell-mediated immunity.[41-56]

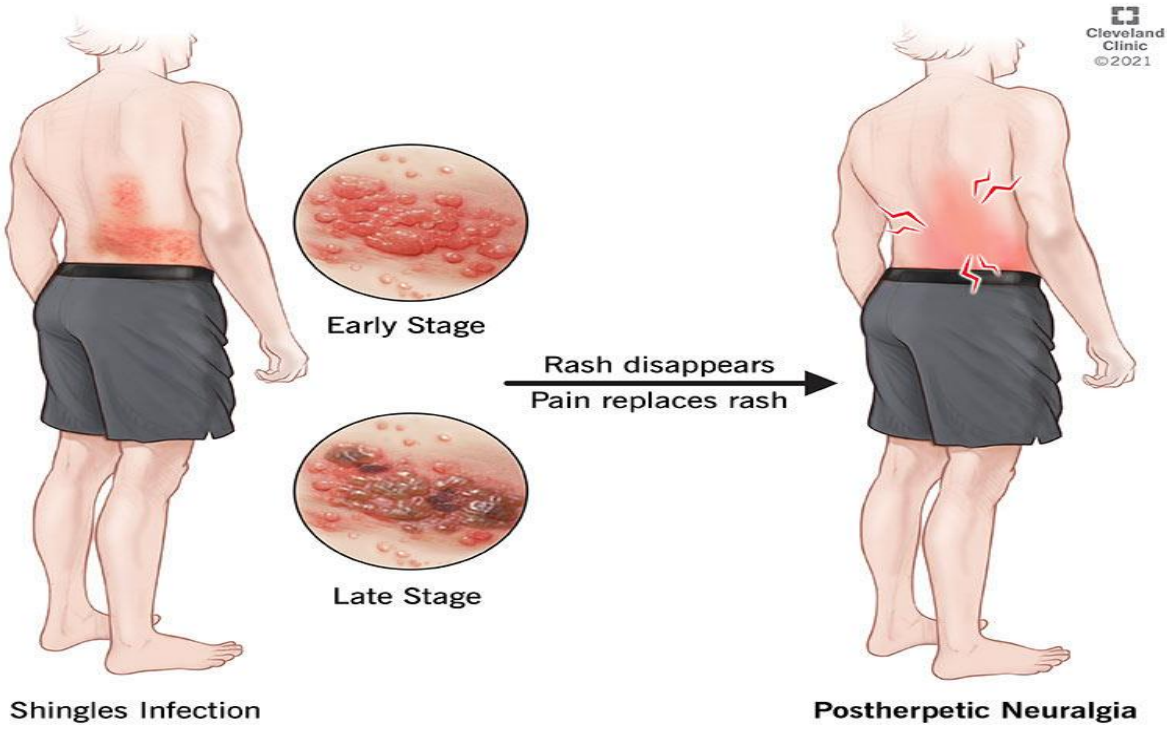
PHN has profound effects on the quality of life of those affected. In a Medline search that looked at studies surveying people affected by PHN, symptoms other than pain that were shown to be associated with the disease included insomnia, depression, fatigue, loss of appetite with subsequent weight loss, and cognitive impairment.[57-58]

In one particular study, 64% of 261 participants reported sleep disturbances; 58% reported negative affects regarding enjoyment of life; and 53% said their general activities were negatively affected.[58]

1.2.4-Clinical manifestations.

Common post-herpetic neuralgia symptoms include:

- Burning, sharp, jagging or aching pain in the area where the shingles rash appeared,
- Itchiness or numbness at or near the area of the former rash,
- Pain that is constant or “comes and goes.” Pain typically lasts, on average, for three months after the rash has healed, but can last for more than a year or longer,
- Pain at affected skin area can be brought on even with a light touch (even clothing brushing against skin),
- Pain gets worse at night or in heat or cold temperatures,
- In rare cases, if the nerve also controls muscle movement, there may be muscle weakness or paralysis.[59-60]



Figure(1-8) Early and late stages of post-herpetic neuralgia.[61]

1.2.5-complications of post-herpetic neuralgia

Post herpetic neuralgia can cause:

- Tiredness.
- Trouble sleeping (insomnia).
- Decreased appetite.
- Poor concentration.

Pain from long-lasting PHN can lead to depression. [61-62]

1.2.6-Diagnosis

A history of HZ and the nature of the pain are critical parameters of a PHN diagnosis, thus, obtaining a detailed medical history and including symptoms and vaccination history are very important, as is performing a careful physical examination with a focus on qualifying the pain and its impact on daily life.[63-64]

Areas previously affected by HZ may show evidence of cutaneous scarring, and the site of the pain should be inspected for rash, color

changes, and edema, area of sensory abnormalities, including allodynia (painful response to normally innocuous stimuli), hyperalgesia (heightened pain response), or dysesthesia (unpleasant and abnormal sensation), in the affected area should be assessed for sensitivity to touch (eg, light touch with a cotton swab or small paintbrush; pinprick with a safety pin or a wooden toothpick), for thermal response to warm or cold objects (eg, metal thermorollers), and/or for response to vibration (eg, using a 128 Hz tuning fork).[63]

Complementary quantitative sensory testing can be used along with bedside examination to provide additional information about the functional status of the somatosensory system.[63-65] Pain intensity and quality should be assessed using an appropriate pain scale, based on the patient's ability to communicate – a numerical rating scale (usually an 11-point scale: from 0, no pain, to 10, severe pain), a visual analog scale, or verbal descriptor scale (eg, McGill Pain Questionnaire).[63] The impact of pain on the quality of life should be evaluated, usually by interview, but structured questionnaires can also be used.[63]

1.2.7-management of the post-herpetic neuralgia (PHN)

1.2.7.1-Prevention of (PHN)

The best way to prevent PHN is to avoid infection with VZV. For children born after the introduction of varicella vaccine in the US in 1995 and who have received the chickenpox vaccination, this is a real possibility.[66] But for adults who contracted chickenpox as children, and who therefore have latent VZV, the best strategy to prevent VZV reactivation is to be vaccinated with the live attenuated shingles vaccine (Zostavax®; Merck & Co, Inc., Whitehouse Station, NJ, USA) approved for use in individuals aged ≥50 years.[67] The vaccine has been shown to be effective in reducing the incidence of HZ, the burden of illness due to infection, and the incidence of PHN. Results of the Shingles Prevention Study involving 38,546 patients aged ≥60 years vaccinated against HZ showed a 61.1% reduction of HZ burden of illness following vaccination compared to placebo.[68] Given the short time the vaccine has been available, there is insufficient data to support its efficacy in the long-term prevention of PHN.[69-70] Also, despite the availability of the vaccine, <30% of adults aged ≥60 years reported having had the vaccination in a 2014 survey.[71]

Prompt treatment of HZ with oral antiviral agents (acyclovir, famciclovir, or valacyclovir) slows the production of the virus and decreases the viral load in the dorsal root ganglia.[31] Although there is some evidence that antiviral therapy may reduce the incidence and severity of PHN, especially when administered early in the disease, the evidence is somewhat inconsistent.[31]

1.2.7.2-Treatment of post herpetic neuralgia.

PHN may persist for years and is difficult to treat. The safety and tolerability of pharmacologic therapies are important issues to consider as PHN affects primarily an older population.[32-33-43] Once PHN has been diagnosed, treatment should be directed at pain control and minimizing treatment-related adverse events, no single best treatment has been identified,

Tricyclic antidepressants (TCAs), gabapentin, and pregabalin are generally the drugs of first choice for the treatment of PHN, current guidelines recommend treatment of PHN in a hierarchical manner, with calcium channel α2-δ ligands (gabapentin and pregabalin), TCAs (amitriptyline, nortriplyline, or desipramine), or topical lidocaine patches as first-line drugs; opioids and topical capsaicin patch or cream as second- or third-line treatment options; or combination therapies with different mechanisms of action (Table1-4).[31-64-69]
Prior to instituting an individual treatment plan, health-care professionals, including nurses, should carefully evaluate patients ' concomitant medications, elderly patients in particular are more likely to have physical and/or cognitive comorbidities, and are more likely to be using other medications.[72] Potential drug interactions occurring in elderly patients may lead to serious or even fatal adverse events.[73]
Adverse responses to medications are more prevalent in the older adult population, and polypharmacy, inappropriate use, and poor compliance are contributing risk factors.[74] Furthermore, many oral medications require careful titration to the optimal dosage and multiple daily dosing, and may be accompanied by bothersome adverse effects.[38-65]
Consequently, patients may not reach the target therapeutic dosage or may stop taking the medication because of side effects.[75] Thus, patients should be educated on appropriate dosing, titration if applicable, the importance of adherence to treatment, and possible side effects, it is also important to set expectations with respect to how long it might take to attain maximum pain relief, to ensure the optimal effectiveness of the treatment, clear communication with the patient, frequent monitoring

of adverse reactions, and patient satisfaction with the treatment are essential.[74] At each patient visit, current pain levels, location of pain, and pain quality should be reassessed, and the patient's ability to perform daily activities should be discussed, response to current interventions and any side effects or difficulties with the treatment regimen should also be discussed.[74]

Tricyclic antidepressants

TCAs such as nortriptyline (Pamelor, Aventyl), desipramine (Norpramin), and amitriptyline (Vanatrip, Elavil, Endep) are used frequently in PHN treatment.[31-64_65-69-76] Although standardly used, TCAs should be used with caution in the elderly,[77] and in those with heart disease, epilepsy, or glaucoma, the practitioner should be familiar with TCA mechanism of action and counsel the patient that it may take weeks for the medication to be fully effective, and that TCAs are associated with significant systemic adverse events (most notably anticholinergic), cardiotoxicity, and other side effects (Table 1-4).[77]

Calcium channel α2-δ ligands

For patients with moderate to severe PHN who have contraindications to or intolerance of TCAs, consider treatment with gabapentin or pregabalin, gabapentin and pregabalin are effective treatments for neuropathic pain, gabapentin, first approved as an anticonvulsant medication,[78] was noted to have beneficial effects on neuropathic pain. Consequently, an immediate-release formulation of gabapentin (Neurontin®; Pfizer, Inc., New York, NY, USA) was approved for the treatment of PHN in 2002.[79] As a result of its nonlinear pharmacokinetics whereby drug absorption and bioavailability decrease with increasing dose, and its short half-life, immediate-release gabapentin is dosed three times daily, in clinical studies, the efficacy of the immediate-release formulation of gabapentin in PHN was demonstrated over a range of dosages from 1,800 mg/day to 3,600 mg/day, but without additional benefit for dosages >1,800 mg/day.[80] Treatment was associated with a high incidence of dizziness and somnolence, which may impact the adherence and/or the ability to achieve a therapeutic dose.[79] A retrospective study of a large medical claims database revealed that only 14% of patients ever reached the therapeutically effective dosage of 1,800 mg/day, and for those who did, it required 10 weeks.[81]

Serotonin norepinephrine reuptake inhibitors

A recent systematic review and meta-analysis of pharmacotherapies for neuropathic pain in adults found a high quality of evidence for the first-line use of the serotonin norepinephrine reuptake inhibitors duloxetine or venlafaxine.[45] However, the recommendation for their use applies to neuropathic pain in general, other guidelines.[37] Recommend the use of serotonin norepinepherine reuptake inhibitors (SNRIs) for painful diabetic neuropathy but not for PHN, citing a paucity of clinical evidence.[76]

Opioid analgesics

The use of opioids in PHN management guidelines has changed from first-line to second- or third-line therapies over time, which likely reflects increasing concern over their potential for misuse, their side effect profiles, and the potential complete response using adjuvant monotherapy.[64-65] Opioids can be used at low doses and titrated to provide relief, possibly while awaiting therapeutic benefits from other first-line agents (ie, tricyclic drugs, gabapentin, or pregabalin), at which point opioids could be tapered off, opioids also can be used cautiously for intractable PHN that is refractory to treatment with other treatments, opioids used in treating PHN pain include oxycodone, morphine, methadone, and tramadol, tramadol has proven less effective than strong opioids in clinical trials for PHN and is considered a mild opioid, while oxycodone, morphine, and methadone are considered strong opioids.[38-64-65-76]

Combination therapies

A treatment plan combining analgesics with different mechanisms of action may provide the best overall therapeutic effect, particularly the combination of an oral agent with topical lidocaine 5% patch, or a combination of gabapentin with opioids or a TCA.[64-76] The combination of the lidocaine 5% patch and pregabalin was effective in patients with PHN who did not previously respond to either medication as monotherapy.[64-69] Side effects were similar to those associated with the lidocaine patch and pregabalin alone, with application-site reactions, dizziness, and somnolence as most common adverse events, also, the combination of immediate-release gabapentin (≤3,600 mg/day) and nortriptyline (≤100 mg/day) was significantly superior in relieving pain to

either treatment as monotherapy in a clinical trial, with no new or higher occurrence of adverse events.[64-69] Finally, combined morphine and immediate-release gabapentin decreased pain more than either medication alone,[64-69] although the clinical meaningfulness of the observed 20% improvement in pain intensity over placebo is modest, and secondary outcome measurements were not consistently superior to either medication as monotherapy, the gabapentin–morphine combination also resulted in a high frequency of adverse events during and after titration period, which included constipation, sedation, dry mouth, vomiting, cognitive dysfunction, dizziness, nausea, ataxia, and edema.[69]

Table(1-4) Treatment options for post herpetic neuralgia.[31-64-69]

Therapy	Dosage	Most common adverse reactions in clinical trials
First line		
Calcium channel α_2-δ ligands		
Gabapentin	Starting dose 100–300 mg at bedtime or 100–300 mg three times daily. Increase dose by 100–300 mg three times every 1–7 days as tolerated up to a maximum of 3,600 mg/day.[a,b,29]	Dizziness, somnolence, peripheral edema, diarrhea, asthenia, infection, dry mouth, constipation, nausea, vomiting, accidental injury, ataxia, abnormal thinking, blurred vision.[c,33]
Gastroretentive gabapentin	Starting dose 300 mg/day. Increase dose by 300 mg/day on days 2, 3, 7, 11, and 15 up to a maximum dose of 1,800 mg/day.[b,35]	Dizziness, somnolence, headache, peripheral edema, diarrhea.[c,35]
Gabapentin enacarbil	Starting dose 600 mg in the morning. Increase dose to 600 mg twice daily on day 4.[b,37]	Dizziness, somnolence, headache, nausea, fatigue/asthenia, peripheral edema, insomnia, weight gain.[c,37]
Pregabalin	Starting dose 50 mg three times daily or 75 mg twice daily as tolerated. Increase dose to 300 mg/day after 3–7 days, and then by 150 mg/day every 3–7 days as tolerated up to a maximum of 600 mg/day.[a,b,29]	Dizziness, somnolence, peripheral edema, ataxia, blurry vision, abnormal gait, headache, weight gain, confusion, edema, abnormal thinking, abnormal vision, pain, accidental injury, constipation, diplopia, amnesia, infection, flatulence, vomiting, incoordination, speech disorder, bronchitis.[c,41]
Tricyclic antidepressants		
Nortriptyline Desipramine	Starting dose 25 mg at bedtime. Increase dose by 25 mg/day every 3–7 days as tolerated up to a maximum of 150 mg/day; if blood concentration of active medication and its metabolite are <100 ng/mL, continue titration with caution.[a,b,29]	Dry mouth, weight gain, drowsiness.[52]
Topical agents		
Lidocaine 5% patch	Apply every 4–12 hours; up to three patches per day.[29]	Application-site reactions (blisters, bruising, burning sensation, depigmentation, dermatitis, discoloration, edema, erythema, exfoliation, irritation, papules, petechiae, pruritus, vesicles), asthenia, confusion, disorientation, dizziness, headache, hyperesthesia, hypoesthesia, lightheadedness, metallic taste, nausea, nervousness, pain exacerbated, paresthesia, somnolence, taste alteration, vomiting, visual disturbances such as blurred vision, flushing, tinnitus, and tremor.[53]
Second or third line		
Opioid analgesics		
Oxycodone	Titration: morphine oral equianalgesic dosages of 10–15 mg every 4 hours; after 1–2 weeks, convert total daily dosage to long-acting opioid analgesic and continue short-acting agent as needed; no maximum dosage, but consider evaluation by a pain specialist at doses ≥120 mg daily or equianalgesic dosage.[29]	Constipation, nausea, somnolence, dizziness, pruritus, vomiting, headache, dry mouth, asthenia, sweating, insomnia, asthenia.[54,55]
Morphine		Constipation, dizziness, sedation, nausea, vomiting, sweating, dysphoria, euphoric mood, somnolence.[56,57]
Methadone		Lightheadedness, dizziness, sedation, nausea, vomiting, and sweating.[58]
Tramadol[a,d]	Starting dose at 50 mg one to two times per day; titrated in 50–100 mg increments in divided doses every 3–7 days; maximum dosage 400 mg/day (100 mg four times per day); maximum dosage for the elderly 300 mg/day.[29]	Dizziness, nausea, constipation, headache, somnolence, flushing, pruritus, vomiting, insomnia, dry mouth, diarrhea, asthenia, postural hypotension, sweating, anorexia.[58]
Topical agents and creams		
Capsaicin 8% patch	Up to four patches for 1 hour every 3 months or longer; needs to be administered by a physician or trained personnel; a topical anesthetic is applied to the affected area before capsaicin patch.[59]	Application-site reactions (pain, burning, erythema, pruritus, papules, edema), nausea, vomiting.[59]
Capsaicin 0.075% cream	Apply three to five times per day.	

Capsaicin (8-methyl-N-vanillyl-6-nonenamide):- is an active component of chili peppers, which are plants belonging to the genus Capsicum,it is a chemical irritant for mammals, including humans, and produces a sensation of burning in any tissue with which it comes into contact.[88]

Figure(1-9)- Chemical structures of Capsaicin.[88]

The exact mechanism of action of topical capsaicin in pain relief is not ,fully understood,

it has long been thought that the pain effects may be due to the reduction of substance P content in the skin. [89]

but the recent studies,, demonstrate that topical capsaicin also causes defunctionalization of upregulated and sensitized TRPV1 receptors on sensory nerve endings.[90-91]

And this is after the discovery of the skin's receptors for heat, cold and pressure by the two scientists who won the 2021 Nobel Prize in Medicine (Ardem Patapoutian and David Julius)

where one of the two scientists discovered (Transient Receptor Potential Channel Subfamily V member 1) or called (TRPV1).[92]

-Capsaicin topical ointments

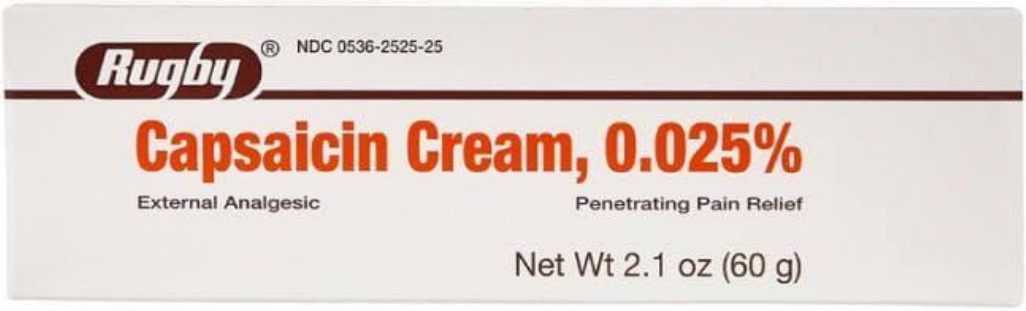


Figure (1-10) Capsaicin Cream,0.025%.[93]

Capsaicin is currently used in topical ointments to relieve the painof peripheral postherpetic neuralgia caused by shingles. It may be

used in concentrations of between 0.025% and 0.075%.[93]

Capsaicin may also be used as a cream for the temporary relief of minor aches and joint pain associated with arthritis, simple backache, strains, Capsaicin topical patch 8%-and sprains.[93]

The 8% capsaicin patch (Qutenza, NeurogesX)

Is a newly available medication for treatment of the neuropathic pain of PHN. Its MOA is initial activation of the TRPV1 on nociceptors that produces pain and erythema,

the consequence of this primary afferent depolariza-tion is partial nociceptor inactivation and corresponding analgesia. [94-97] In 2 double-blind, randomized studies of 402 and 416 subjects with mean PHN duration of approximately 3 to 4 years, 44% and 47% of patients,respectively, experienced 30% or greater pain reduction. This was a statistically significant improvement

over the response to 0.04% capsaicin patch that served as an active control.[94]

The 8% capsaicin patch is designed to be applied over the painful area for 60 minutes every 90 days after appropriate local anesthetic application to the skin,except for the local application-site pain, related blood pressure elevation, and transient skin reaction, the 8% capsaicin patch is generally well tolerated and allows up to 3 months of clinical improvement with potentially

less reliance on oral analgesics.[94] An adequate number of patches needs to be prescribed to cover the painful dermatome, not to exceed 4 patches the application site pain increases proportionately with the number of patches applied, therefore, adequate anesthetizing of

the skin is critical to a successful 60-minute application,there are no end-organ effects of or contraindications to capsaicin, because of its recent availability, the role of the 8% capsaicin patch within the treatment spectrum is not well established,however, given its safety, procedural

simplicity, and potential to decrease opioid and anticonvulsant use, it can be offered to patients to potentially reduce oral analgesic consumption, related side effects, and end-organ effects, as well as ,improve treat-ment adherence

interventional procedures often are limited to refractory disease, analgesic failures, or

circumstances where prompt relief is psychologically necessarythey also can be used to reduce reliance on analgesics,there is inadequate evidence to support the use of TENS to treat PHN, TENS works by stimulating the cutaneous nerve fibers with mild current, with adjustments in frequency, intensity, and pulse durations. [95-96]

Side Effect of Capsaicin

:Both creams and patches can irritate your skin and cause problems like

Redness and swelling

Soreness •

Dryness •

Burning and itching •

Pain • [96]

contraindications of uses capsaicin

(skin wound)(open wound)

skin irritation

eyes

mouth

genitals.[96]

Epidural and intrathecal steroids injection

Noninvasive management practices, which are widely used for PHN, have not been consistently effective.[98-99] Invasive treatment options have been developed, including local infiltration, sympathetic nerve blocks, and intrathecal injections. However, the reported efficacy of the invasive methods also is inconsistent.[100-101]

Epidural steroid injection (ESI) with the trans foraminal and interlaminar administration of steroids and local aesthetics is among the more common treatments for patients with refractory PHN, however, its effectiveness is controversial, to our knowledge, the only study investigating factors associated with improved efficacy of transforaminal SI for PHN reported a symptom duration of 3 months as the only significant predictor of benefit. 102 The thespecific aims of the present study were to seek other factors associated with the efficacy of ESI in our patient population with PHN and to report our experience for ,therapeutic success with ESI

Preservative-free intrathecal methylprednisolone has been shown to provide superior pain relief

compared with intrathecal lidocaine and epidural methylprednisolone.[103-104]

The patients were randomized to receive intrathecal methylprednisolone plus lidocaine (once weekly for 4 weeks), intrathecal lidocaine alone, or no intrathecal treatment, at every follow-up interval (4 weeks, 1 year, and 2 years), the proportion of patients with good-to-excellent pain relief was markedly higher in the steroid group (about 90 percent) than in the other 2 groups (less than 10 percent), No complications were reported, Cerebrospinal fluid concentrations of interleukin-8 (a known marker for inflammatory pain) dropped significantly in the methylprednisolone group but remained unchanged in the other 2 groups.[105-106]

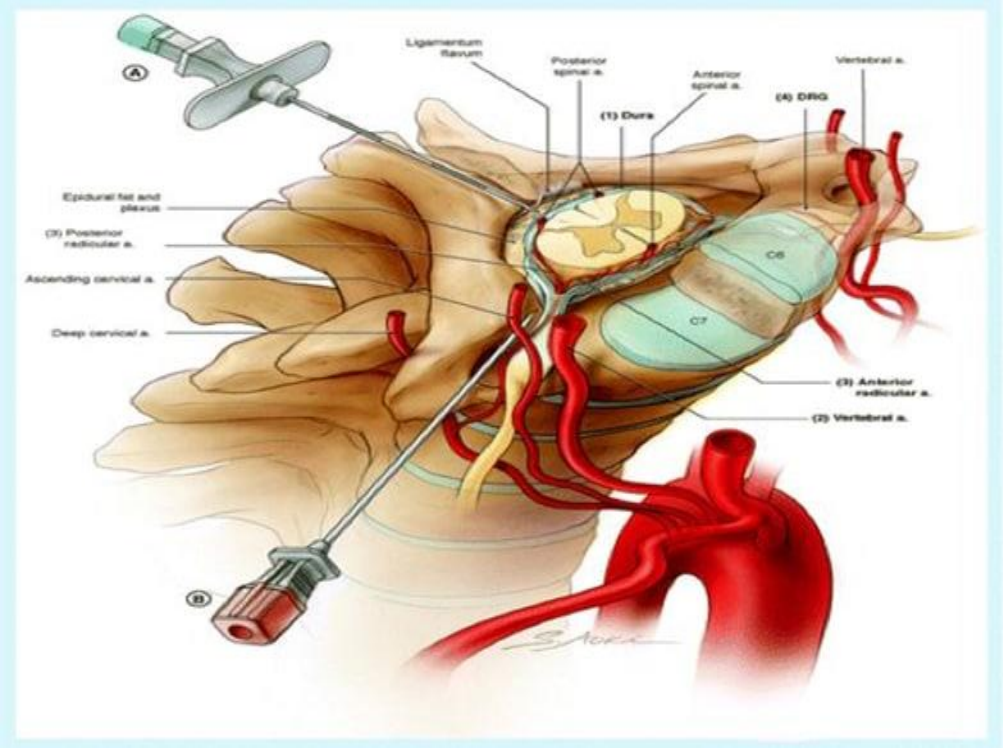
(Dorasal root entry zone (DREZ) lesion or(DREZ-otomy))

is considered an effective treatment for chronic pain due to spinal cord injuries, brachial and lumbosacral plexus injuries, postherpetic neuralgia, spasticity, and other conditions, the objective of the technique is to cause a selective destruction of the afferent pain fibers located in the dorsal region of the spinal cord.[109-110]

However, a complication rate as high as 23.58% was reported.[111]

,Efficacy - Improvement rate is 20% in long-term studies

Complications - Gait disturbances are experienced by 12% of treated patients.[112]



Figure(1-11)Dorsal root entry zone lesion.[112-113]

Botulinum toxin:

The use of Botulinum toxin a for treating post-herpetic neuralgia produced very promising results with very few adverse reactions. BTX-A can be considered as a valid approach in the treatment of PNH, especially in patients that do not respond well to painkillers.[114]

Several mechanisms of pain reduction by Botulinum toxin

assuming an inhibitory effect on the release of various inflammation-mediated

substances (e.g., substance P, glutamate, calcitonin gene-related peptide). This inhibitory

effect is mediated by blocking exocytosis by Botulinum toxin.[115]

Botulinum toxin BTX-A could be an alternative therapeutic modality in treating PHN in the future,

however, further randomized, controlled trials are needed to confirm the analgesic efficacy of BTX A, and to determine its role in the overall treatment of patients with PHN.[116]

Conclusion :

1-Post herpetic neuralgia is associated to complex pathophysiologic phenomena and to worsening of quality of life, a commonly used definition of delineating PHN is suggested by Dworkin as a “significant pain or abnormal sensation 120 days or more after the presence of the initial rash.

2-The pathophysiology behind PHN is a neuronal injury that affects both the peripheral and central components of the nervous system.

3-VZV is a highly contagious DNA virus that remains latent within the sensory ganglia following resolution of chickenpox, which usually occurs during childhood.33 During HZ, VZV is reactivated, travels back along the affected neurons away from the sensory ganglia.

4-Risk factors for developing PHN after a herpes zoster infection include older age, immunosuppression, female gender, greater acute pain and dermatomal injury, and severe prodrome.

5-Common post-herpetic neuralgia symptoms include

Burning, sharp, jagging or aching pain in the area where the shingles rash appeared

6-The best way to prevent PHN is to avoid infection with VZV. For children born after the introduction of varicella vaccine and who have received the chickenpox vaccination.

7-PHN treatment involves specific driugs for neurapathic pain.

Physicians and patients must be educated about the importance of instituting immediate treatment being that

pain specialists must be called in the acute HZ phase and not only when PHN is already installed.

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