Herpes-zoster and post-herpetic neuralgia*

**ABSTRACT**

**BACKGROUND AND OBJECTIVES:** Herpes-zoster (HZ) is a vesicular painful skin rash resulting from the reactivation of varicella-zoster virus (VZV) in dorsal root ganglia or cranial nerves, which occurs decades after the primary varicella infection. However, even after skin healing, pain may persist for months or even years. This is a complication known as post-herpetic neuralgia (PHN). This review aimed at giving an overview of herpes-zoster and PHN clinical history, focusing on pain control.

**CONTENTS:** PHN is characterized by chronic neuropathic pain. Its incidence is higher among the elderly and immunocompromised individuals. There are several treatment options, which may be pharmacological or interventionist, both with variable efficacy.

**CONCLUSION:** Pain affects quality of life of patients, interfering with their daily activities. In spite of advances already obtained in the analgesic therapy for HZ and PHN, there are still difficulties in its approach. So, it is very important to prevent, diagnose and early treat HZ and its complications.

**Keywords:** Herpes-zoster, Post-herpetic neuralgia.

INTRODUCTION

Varicella-zoster virus (VZV) is a herpes virus causing varicella, which latently persists in the nervous system throughout the life of individuals after primary infection. Herpes-zoster (HZ) is a relatively common infectious disease caused by the reactivation of VZV and is characterized by painful skin manifestations. The disease may evolve to healing in a few weeks or pain may persist for months or even years. Post-herpetic neuralgia (PHN) is a term used to define the persistence of pain. Pain is the most uncomfortable symptom for patients, both acute pain associated to HZ and PHN chronic pain. Pain persistence significantly impairs quality of life (QL) and increases health care costs. Currently, several approaches and interventionist techniques are available to control pain. In spite of the advances of the analgesic therapy for HZ and PHN, there are still difficulties with their approach, being some patients refractory to treatment. This study aimed at addressing an overview of the clinical history of HZ and PHN focusing on pain control.

**HERPES-ZOSTER**

**Etiology and clinical manifestation**

HZ is caused by the reactivation of VZV in cranial nerves and dorsal root ganglia, in general triggered decades after primary varicella infection. When VZV-specific cell immunity is compromised, the disease is triggered. Reactivation is more common in individuals immunocompromised by other diseases, such as cancer, acquired immunodeficiency...
syndrome, post-transplant immunosuppression and chemotherapy. There is a strong correlation between higher incidence of HZ and older age, especially above 55 years of age, because older age is associated to a decrease in T-cell-mediated immune response mediated.

Clinical manifestation starts with mild to moderate skin burning in a certain dermatome, often followed by fever, shivering, headache and malaise, and progresses to erythematous maculopapular rash until the final stage of crusts.

The anatomic pattern follows a peripheral distribution in the pathway of involved nerves, is normally unilateral and circumscribed to a dermatome; however, it may involve two or more dermatomes. There is predominance on chest and face.

Some patients may present just radicular pain, characteristic of HZ, without developing skin lesions and this manifestation is clinically called herpes sine herpete, which may be more severe than usual manifestations affecting different nervous system levels.

The disease is treated with antiviral drugs which accelerate skin eruptions healing, decrease acute pain intensity and duration and probably prevent PHN. However, some patients will develop PHN even after having adequately received antiviral drugs.

The three mentioned antiviral drugs have similar success rates and are well tolerated. Most common side effects are: abdominal pain, nausea, vomiting, headache and dizziness. Antiviral therapy is especially important for immunocompromised patients because they are at increased risk for skin and visceral dissemination and neurological complications.

Treatment

HZ diagnosis is difficult during early stages of the disease because it may take up to three weeks for the appearance of skin lesions, thus delaying the beginning of the treatment. The anatomic pattern follows a peripheral distribution in the pathway of involved nerves, is normally unilateral and circumscribed to a dermatome; however, it may involve two or more dermatomes. There is predominance on chest and face.

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Currently, this type of disease is more easily diagnosed by the polymerase chain reaction – PCR technique to amplify VZV virus. The material used for PCR may be collected from skin biopsy, vesicular fluid, saliva or CSF. So, VZV may reach cranial nerves and lead to major complications. Trigeminal nerve involvement may cause alterations on face, mouth, eyes or tongue. Ramsay-Hunt syndrome is an uncommon manifestation and involves facial nerve geniculate ganglion causing earache and facial paralysis.

There are other HZ complications such as: encephalitis, myelitis and peripheral nerve paralysis. These complications are more common in immunocompromised individuals. HZ may become generalized, suggesting immune impairment or the presence of neoplasia. So, it is important to rule out such possibilities.

Although controversial, studies indicate that the incidence of PHN increases in proportion and severity when the acute stage is inadequately treated. HZ recurrence is very uncommon and affects approximately 5% of patients. One explanation is that HZ would stimulate an important immune response, thus preventing subsequent episodes.

POST-HERPETIC NEURALGIA

Definition

PHN is characterized by chronic neuropathic pain persisting at least one month in the pathway of the affected nerve, starting between one and six months after skin rash healing and may last for years. The incidence of PHN varies from 10% to 20% in immunocompetent adults. There is no predominance with regard to gender. Age is a major PHN predictor because prevalence significantly increases with age.

Pain may be divided into three different stages: acute, subacute and chronic. The acute stage is defined as pain starting within 30 days after the appearance of skin rashes. The
sub-acute stage is characterized by pain persisting beyond
the acute stage, but resolved before PHN diagnosis4,5,10. The
third stage is PHN itself, with pain persisting for 120 days or
more after the exanthema19.

Clinical manifestation and diagnosis
PHN may manifest with different types of pain13,14 and sen-
sory symptoms8. Pain is chronic, characterized by burning or
pricking and may be associated to hyperalgesia, hyperesthesia
or allodynia14. Excruciating, pinching or stabbing pain has
been more often reported in acute HZ, and burning pain is
more common in PHN4,5,7,8.
The anatomic distribution of PHN follows the pattern of der-
matomes involved with HZ, being dermatomes from T₃ to L₃
more commonly involved7. HZ affects chest and face in 50%
to 60% of cases and sacral dermatomes are involved in just
5%, thus being a more uncommon site for the appearance of
PHN8,24.
HZ and PHN diagnosis is clinical. Differential diagnosis will
depend on pain clinical characteristics and location of the af-
fected nerve. Differential diagnosis includes: cardiac diseases,
Bell paralysis and trigeminal neuralgia, among others7,8.
Risk factors for PHN are: more advanced age, higher intensity
of pain and exanthema in the acute stage, presence of negative
sensory signals, presentation of polynuropathy on active HZ
and psychological aspects. The impact on personal and social
life of patients is considerable because it affects sleep and the
ability to work and perform physical activities, thus affecting
their QL4,8,10. PHN may significantly affect several aspects of
the life of a patient, causing chronic fatigue, sleep disorders,
difficulty to concentrate, depression and anxiety, anorexia,
weight loss and social withdrawal4.

Treatment
Treatment should be with drugs to control and relieve pain.
First line drugs to treat PHN are anticonvulsants (gabapentin
and pregabalin) and tricyclic antidepressants (especially ami-
triptyline). Opioids are classified as second line analgesics and
may also be used4,8,10,23.
Although there are several pharmacological treatments for
symptomatic relief of neuropathic pain, many times these
agents do not offer satisfactory relief for all patients21. The
complex and heterogeneous nature of PHN suggests that ad-
equate pain relief with a single medication is unlikely. Anal-
egesic combinations are used in the clinical practice for pain
relief9.

Pharmacological treatment

Tricyclic antidepressants
Low dose tricyclic antidepressants are used for PHN as single
therapy or associated to other drugs5,10,14,23. Your use demand
3 monts to positive effect10. Action mechanism is the block-
ade of serotonin and norepinephrine reuptake and also the
inhibition of voltage-dependent sodium channels4,10,23.
Amitriptyline is the most common drug17, however all drugs
have similar therapeutic efficacy. Tricyclic antidepressants
prescribed for HZ include amitriptyline, nortriptyline, impip-
ramine and desipramine19.
Tricyclic antidepressants should be selected based on the
particularities of drugs and comorbidities of each patient. A
special concern are elderly patients, more susceptible to hav-
ing pharmacological interactions4,10. A limiting factor for the
clinical use are adverse effects such as dry mouth, blurred vi-
sion, dizziness, fatigue, sedation, urinary retention, constipa-
tion, weight gain, palpitations, orthostatic hypotension and
prolonged QT interval. Although there is no formal recom-
mandation to request an electrocardiogram (ECG) before
starting therapy with tricyclic antidepressants, it is prudent
to get an ECG from patients with cardiac disease10,23.

Anticonvulsants
Anticonvulsant drugs have been used for different conditions
inducing neuropathic pain4,13. Gabapentin and pregabalin
are drugs analog to gamma aminobutyric acid (GABA), how-
ever they do not act on GABA receptor. Gabapentin action
mechanism is unclear, but it is believed that it acts on the
α-2-δ sub-unit of voltage-dependent calcium channels, de-
creasing calcium flow and inhibiting excitatory neurotrans-
mitters release on primary afferents of spinal cord dorsal
horn, similarly to pregabalin5,10,23.
It is possible that gabapentin has effect on N-methyl-D-as-
partate type receptors (NMDA), decreasing glutamate levels
to better control allodynia. Daily gabapentin dose may vary
from 1800-2400 mg13. It is totally excreted by the urine. Ma-
ajor side effects are: sleepiness, dizziness, ataxia and per-
ipheral edema5,10. The combination of gabapentin and an opioid,
both in lower doses, induces superior analgesia as compared
to each drug used as single agent10.
Pregabalin is effective and safe for PHN because it controls
pain and has minor interaction with other drugs. Recom-
manded dose is 300-600 mg/day10,14. Its side effects are in
general not severe, but may happen, such as peripheral ede-
ma, dizziness and sleepiness10.
Carbamazepine acts by antagonizing sodium channels, stabi-
lizing pre and post-synaptic neuronal membranes. It is used
for several diseases inducing neuropathic pain5,17. It is very
effective for paroxysmal13,14 and excruciating pain and less ef-
fective for burning pain and allodynia. Recommended dose
is 600-1600 mg/day divided in 2 to 3 doses6. Adverse effects
associated to carbamazepine are dizziness, blurred vision,
nausea and vomiting17. There might be skin rash, however
severe reactions such as Stevens-Johnson and toxic epidermal
necrolysis are uncommon5,3.

Opioids
Several studies have shown that opioids are effective to treat
neuropathic pain, especially if pain is moderate to severe; how-
however some considerations must be done, such as dose ti-
tration to minimize side effects, drug tolerance and abuse.
Opioids should be rationally used4,5. Adverse effects, such as
nausea, vomiting, obstipation, dizziness and sedation should
be taken into consideration. A common recommendation is to use codeine (30-60 mg) every 6 hours, when needed. Codeine may be associated to paracetamol. Other opioids (morphine, oxycodone, methadone) are also used. Tramadol analgesic action occurs in μ-agonist opioid receptors and in norepinephrine and serotonin reuptake inhibition, promoting pain relief and improved QL. In cases of difficult pain management, a combination of tramadol and amitriptyline has been used.

**Capsaicin**
Capsaicin is a pepper-derived alkaloid (Capsicum frutescens) acting on neuropathic pain induced by substance P peripheral sensitization on primary peripheral receptors, leading to painful symptoms. Capsaicin stimulates a peripheral discharge of substance P, leading to its storage depletion. The unavailability of substance P on primary afferent fibers (C fibers) inhibits the generation of the painful phenomenon. During early topical treatment with capsaicin there is increased pain, especially burning pain, due to substance P discharge before its depletion. Very often this impairs adherence to treatment. However, this inconvenient effect decreases or disappears with time. It has been shown that topical capsaicin provides significant pain relief in randomized clinical trials. Topical capsaicin in low concentration (0.025%-0.075%) has been used for decades as second line treatment for PHN, however with diverging results. Recently, 8% topical capsaicin has been developed and approved for the treatment of PHN, based on two randomized and controlled studies which have shown the efficacy and safety of 1-hour application for PHN. It is applied by transdermal route on the painful area for 30 minutes on feet and for 60 minutes on remaining body areas. Treatment may be repeated every 3 months and its adverse effects are pain and erythema on application site, so it needs topical anesthesia before application. It should not be applied to injured or inflamed skin. This treatment may decrease pain for several months; however 8% capsaicin patch has not been studied for trigeminal PHN and for face and head application. 8% capsaicin is not available in Brazil.

**Lidocaine**
Topical lidocaine is a first line drug to treat PHN. It acts by blocking sodium channels and decreasing abnormal ectopic discharges. It is used as 5% lidocaine skin patches or as a cream, such as the Eutectic Mixture of Local Anesthetics (EMLA) containing 2.5% prilocaine and 2.5% lidocaine. 5% lidocaine patch is licensed for PHN patients in the USA. The patch has 750 mg lidocaine, of which just 5% are released. Topical lidocaine is effective and safe, with low incidence of systemic adverse reactions and few side effects; in general, patients have mild local reactions. Even with multiple lidocaine applications, systemic levels of this drug remain low. 5% lidocaine should be applied in the painful skin area for a maximum period of 12h per day. It may be used in association with anticonvulsants, opioids and tricyclic antidepressants.

**Interventionist treatment**
There are many interventionist options as strategy to treat PHN, however some with uncertain efficacy.

**Neural blocks**
Sympathetic neural blocks may also be considered to relief HZ and PHN acute pain. Although the precise mechanisms through which sympathetic nervous system contributes to neuropathic pain are not clear, data indicate an abnormal activation of alpha-adrenergic receptors in primary afferent neurons. Neural blocks have been used to relieve pain in PHN patients, although with less analgesic efficacy as compared to HZ. When the blockade is induced during HZ acute stage, in addition to decreasing pain intensity, it theoretically prevents the development of PHN.

Local anesthetics promote pain relief for 12-24 hours. In the long term, relief may be achieved by weekly performing the procedure in early stages of the disease. The incidence of severe complications induced by the blockade is low and depends on the location of the blocked nerve. A single administration in the epidural space of a steroid associated to local anesthetic during HZ acute stage may decrease pain for one month, but it is not effective for the long term prevention of PHN.

Several observational and prospective studies suggest that epidural block in combination with oral administration of an antiviral drug is very effective to treat acute HZ, decreasing pain duration and severity. Other nervous blocks, such as intercostal nerve block, have been used to relieve PHN pain. Although subarachnoid injection of methylprednisolone acetate relieves PHN pain, its safety has been questioned, since it contains benzyl alcohol and polyethylene glycol as preservatives.

**Spinal cord stimulation**
Spinal cord stimulation has been used to treat chronic neuropathic pain, but its action mechanism is still unclear. Its action is based on the pain control gate theory, where the stimulation of myelinated Aβ fibers interferes with the transmission of nociceptive stimuli conducted by C and Aδ fibers from the periphery to the spinal cord dorsal horn. The electric impulse is transmitted as from a generator implanted in the subcutaneous to electrodes placed in the epidural space. Spinal cord stimulation has complication rates varying from 30% to 40%.

Major complications are: hardware problems, especially electrodes migration, infection and painful stimulation. Complications are more significant when associated to neurological injuries due to root or spinal cord injury in the perioperative period. In the attempt to prevent infection, a strict sterile technique and venous antibiotics are used before the procedure. There may be accidental dura-mater puncture during the implant of the spinal cord stimulator, resulting in postdural puncture headache. The first option is the conservative treatment; however for refractory cases it is recommended an...
epidural blood patch. When there is painful stimulation, one should reposition or remove the electrode\(^5\). Current literature evidences suggest that spinal cord stimulation is effective to handle certain types of neuropathic pain. For some patients, it may promote long term pain relief in up to 60% to 80%\(^6,10,23\), with improved patients’ QL and satisfaction.

**Surgical excision**

Preliminary studies have tried to show that surgical skin excision of the area affected by PHN is an option to decrease pain, eliminate tactile allodynia and decrease the use of analgesics in up to one year after surgery, but follow up has revealed constant pain increase, exceeding pre-surgical levels. Authors have concluded that surgical skin resection of the affected area is not recommended to treat PHN\(^5,8,10\).

**Acupuncture**

This is a therapy considered effective to control pain. In spite of several documented cases about its use for HZ and PHN, samples are small. It is very useful when jointly used with conventional PHN therapies\(^4,7,8\).

**Psychological treatment and behavioral therapies**

The association of emotional and biological factors is extremely important for PHN maintenance and modulation\(^5\). So, potential benefits of psychological support for PHN patients should not be ignored\(^4,5\). Behavioral therapies, such as relaxation, meditation and massages have also been used with positive effects for PHN\(^4,5\).

**Prevention**

The number of HZ and PHN patients may increase in the future, because general population is ageing, which may increase the incidence of HZ and its complications\(^5\). A prophylactic vaccine able to improve specific immunity of T cells against VZV is a promising clinical approach to limit HZ and its debilitating complications, including PHN. In fact, HZ is associated to increase in specific cell immunity for VZV, being uncommon recurrences of HZ in immunocompetent individuals\(^9\).

The study about HZ prevention, Shingles Prevention Study (SPS), has evaluated the efficacy of an attenuated live virus vaccine to decrease the incidence and/or severity of HZ and PHN in a sample of 38546 individuals aged ≥60 years. The vaccine is effective to prevent HZ and promotes 66.5% decrease in the incidence of PHN and of 51.3% in the incidence of HZ\(^21,29\).

This vaccine was approved by the FDA (US Food and Drug Administration) and by EMA (European Medicines Agency). The vaccine is indicated to prevent HZ in individuals aged ≥60 years (USA) or ≥50 years (Europe), being contra-indicated for immunocompromised patients, children and pregnant women\(^4,21\). In the future, vaccines against varicella and HZ may change HZ and PHN epidemiology and natural history\(^4\). However, vaccine against HZ is still not available in Brazil\(^33\).

**CONCLUSION**

Acute pain is the symptom afflicting HZ patients the most. Early use of antiviral drugs accelerates the healing of skin rashes and decreases pain intensity. Early HZ diagnosis and treatment are important in the attempt to optimize pain management in the acute stage and to prevent complications, such as PHN. Several therapeutic options are available to treat PHN, however with variable efficacy. Optimal pain control is difficult and no treatment is completely effective for all patients.

Analgesic combinations are used in the clinical practice for pain relief. However, randomized and controlled clinical trials are needed to better evaluate drug combinations and new therapies, aiming at developing new strategies to manage PHN. A prophylactic vaccine against VZV is a promising approach to decrease the incidence of HZ and PHN.

**REFERENCES**

24. Bjekic M, Markovic M, Sipietic S. Penile herpes zoster: an unusual location for a com-