

Post-herpetic neuralgia

Neuralgia pós-herpética

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ABSTRACT

BACKGROUND AND OBJECTIVES: Post-herpetic neuralgia is defined as pain persisting for more than three months after the resolution of skin eruptions observed in herpes-zoster. Post-herpetic neuralgia incidence is quite variable, increases with age, being more frequent among patients aged over 60, and is associated to reduced quality of life of affected individuals. The objective of this review is to discuss key aspects of post-herpetic neuralgia, particularly its pathophysiology, clinical signs, diagnosis, prevention and treatment.

CONTENTS: Post-herpetic neuralgia pathophysiology is poorly understood and involves peripheral and central nervous system mechanisms. Associated clinical signs are variable and represented mainly by pain with neuropathic features and skin changes in dermatomes previously affected by herpes-zoster. Post-herpetic neuralgia prophylactic vaccination seems to be the best preventive option. Diagnosis of post-herpetic neuralgia is largely clinical and treatment involves an early-stage, multimodal approach. Among techniques described in the literature, there is pharmacological treatment which, when not effective, requires the implementation of interventional techniques.

CONCLUSION: Post-herpetic neuralgia is a complex entity and should be treated in a multidisciplinary way aiming at improving patients' quality of life.

Keywords: Chronic pain, Clinical features, Diagnosis, Pathophysiology, Post-herpetic neuralgia, Prevention, Treatment approaches.

RESUMO

JUSTIFICATIVA E OBJETIVOS: A neuralgia pós-herpética é conceituada como dor persistente por mais de três meses após a resolução das lesões de pele observadas no herpes-zoster. A incidência de neuralgia pós-herpética é bastante variável e dependente da idade, sendo mais frequente em pacientes acima de 60 anos e associada a redução da qualidade de vida do indivíduo. O objetivo deste estudo foi discutir os principais aspectos da neuralgia pós-herpética, atentando para a sua fisiopatologia, manifestações clínicas, diagnóstico, prevenção e tratamento.

CONTEÚDO: A fisiopatologia da neuralgia pós-herpética é pobremente compreendida e envolve mecanismos periféricos e centrais. As manifestações clínicas a ela associadas são variáveis e representadas principalmente por dor com característica neuropática e alterações de pele no dermatomo acometido anteriormente pelo herpes-zoster. A vacinação profilática para a neuralgia pós-herpética parece ser a melhor opção para preveni-la. O seu diagnóstico é eminentemente clínico e o seu tratamento envolve a necessidade de uma abordagem precoce e multimodal. Dentre as técnicas descritas encontram-se o tratamento farmacológico e, quando este não é efetivo, a implementação de técnicas intervencionistas.

CONCLUSÃO: A neuralgia pós-herpética é uma entidade complexa que deve ser tratada de forma multidisciplinar com o intuito de aumentar a qualidade de vida dos pacientes.

Descritores: Diagnóstico, Dor crônica, Fisiopatologia, Manifestações clínicas, Neuralgia pós-prevenção, Tratamento.

INTRODUCTION

Post-herpetic neuralgia (PHN) is pain persisting for more than three months after resolution of skin injuries observed in herpes-zoster (HZ). HZ is painful rash in dermatome distribution. After primary infection with varicella, virus remains quiescent in cranial sensory nerves ganglia and in spinal dorsal root ganglia. Cell immunity for varicella-zoster virus decreases with age or due to immunosuppression. In this situation, virus is reactivated and migrates from affected sensory nerves to the skin, causing pain prodromes, followed by skin rash and erythema.

It is estimated that one out of three individuals shall develop HZ during life¹. Location and distribution of injuries on the skin are different. Typically, HZ is unilateral, does not cross midline and is located in a single dermatome, with adjacent dermatomes affected in 20% of cases². Most commonly affected dermatomes are those in the thoracic region and trigeminal nerve ophthalmic branch. HZ neurological complications may include acute or chronic encephalitis, myelitis, aseptic meningitis, motor neuropathies, Guillain-Barré syndrome, hemiparesis and peripheral or cranial nerves paralysis^{3,4}. Most common complications include bacterial infection by *Staphylococcus aureus* or *Streptococcus pyogenes*, scar formation and hyperpigmentation.

PHN is a described complication and deserves attention for its high frequency and negative impact on quality of life. Studies have shown that the incidence of PHN is variable and age-dependent, being 5% in patients below 60 years of age, 10% in individuals from 60 to 69 years of age and 20% in those above 80 years of age⁵.

This review aimed at discussing major PHN aspects, with attention to its pathophysiology, clinical manifestations, diagnosis, prevention and treatment.

PATHOPHYSIOLOGY OF POST-HERPETIC NEURALGIA

PHN pathophysiology is poorly understood. The replication of varicella-zoster virus latent in sensory ganglion results in peripheral and central nervous systems (PNS, CNS) injury. Different pathophysiologic processes seem to be involved with the development of HZ and PHN^{6,7}. Studies have shown that in acute HZ, skin is inflamed and partially denervated. This initial inflammatory process has variable duration, and may persist for weeks or even months. Inflammatory mediators, such as bradykinin, substance P, histamine, cytokines and H⁺ ions are released after tissue injury, contributing to the activation of nociceptors and to decrease pain threshold. Peripheral sensitization process starts with consequent exacerbation of response to noxious and non-noxious stimuli⁸.

In dorsal root ganglion there is inflammation, hemorrhagic necrosis and neural loss, especially of C fibers⁹. As a consequence, there is sprouting of A-beta fibers at afferent C fibers connection site, expanding neuron receptive field and helping the interpretation of harmless peripheral mechanical stimuli as aggressive, phenomenon known as mechanical allodynia, often observed in PHN patients. It is believed that allodynia and sensory loss in the affected dermatome are associated to the deafferentation phenomenon, which is consequence of reorganization of dorsal spine receptive fields⁷.

Nervous A-delta and C fibers are primarily involved in nociception and A-beta fibers are related to sensation of touch. These fibers leave periphery and travel to spinal cord posterior horn, which is organized in laminar form. Rexed laminae are numbered from I to X. In physiologic situation, laminae I, II and V are responsible for pain stimulus transmission, while adjacent laminae are associated to sensation of touch transmission. In the presence of neural injury, there is receptive fields reorganization, allowing that a touch stimulus be

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perceived and interpreted by the body as being pain information. A-beta fibers connect with spinal tracts transmitters of painful sensations and originate sensory changes and allodynia.

Normal nervous system signaling process is altered in PHN. It is believed that the sprouting of sympathetic noradrenergic axons in dorsal root ganglion, around A-delta fibers, is responsible for the activation of sensory afferent fibers after sympathetic stimulation¹⁰. In addition, the loss of gabaergic neurons and injury in elements making up the descending inhibitory pain system contribute to increased sensitivity in the affected area.

CLINICAL MANIFESTATIONS

PHN may have different forms, although none is pathognomonic. Pain may be constant or intermittent and be reported as burning, throbbing, cutting, penetrating or shock pain. It may be evoked by tactile stimuli, which characterizes allodynia. This is often debilitating, impairing patients' quality of life¹¹.

Baron et al.¹² have carried out a cohort study with 2100 patients with PHN or painful diabetic neuropathy (PDN). They have observed that allodynia was present in 50% of PHN patients and in 18% of PDN patients. It is important to mention that the frequency of allodynia found in this review was lower than that mentioned in published clinical trials where 90% of PHN patients had allodynia.

Sensitivity changes, such as paresthesia, dysesthesia, thermal or mechanical hyperalgesia have been described¹².

There might be musculoskeletal pain in PHN patients as result of excessive protection of the affected area. Myofascial trigger points, atrophy and decreased joint movement amplitude have been observed¹³. Some patients have chronic itching, which persists or appears after HZ, impairing their quality of life¹⁴.

At physical evaluation, there are areas of hyperpigmentation, hypopigmentation or scars in dermatomes previously affected by HZ. Redness and brownish tone have also been described¹³.

Although less studied, motor function alteration may be present in PHN patients and may persist after skin erythema resolution. An example is facial paralysis evidenced by ptosis and nasolabial groove erasure after facial nerve involvement¹³.

DIAGNOSIS

PHN diagnosis is predominantly clinical. History of HZ and persistent pain in affected dermatome defines this clinical entity¹³.

Some patients report a quiescent period between HZ pain resolution and onset of PHN-associated pain. In a study with 156 patients, Watson et al. have observed that 25% of individuals with poor outcome had little or no pain¹⁵.

Pain recurrence in affected dermatome is not only associated to recurrent HZ, but may coincide with changes in emotional or physical status of patients¹⁴.

There might not be a clear history of skin erythema. In this case, final PHN diagnosis requires serial serum evaluation where the presence of HZ virus DNA (VZV-DNA) or anti-VZV antibody should be looked for in the CSF¹⁶.

It is important to emphasize that complete PHN diagnosis involves the observation of its impact on quality of life. It is known that PHN has potential to impair patients' physical, emotional and social performance, even leading to psychiatric comorbidities¹⁷.

LABORATORY DIAGNOSIS

Diagnostic tests have limited application in the clinical management of PHN patients. A variety of studies has been used in clinical research environments. Among them there are quantitative sensory test (QST), skin biopsy and nervous conduction studies. QST is applicable for the identification of phenotype subtype in PHN patients. It is believed that in the future this information might orient PHN treatment, which would start to be based on the understanding of involved pathophysiologic mechanisms¹⁸.

PREVENTION

Still controversial, the use of antiviral drugs in acute HZ phase raises the hypothesis of interrupting viral replication, reducing nervous injuries and, by consequence, the appearance of PHN. Vander Straten et al.¹⁹ have observed that the use of antiviral drugs in the acute phase was effective to decrease PHN severity and duration, but not its incidence. Dworkin et al.²⁰, in turn, have observed that people with HZ not receiving antiviral drugs in the acute phase had significantly higher incidence of PHN.

PHN prevention is closely related to HZ prevention. Preventive measures include children vaccination against varicella-zoster virus, passive immunization against varicella (varicella-zoster immune globulin – VZIG) and vaccination against herpes-zoster for adults.

Children vaccination

Children should be vaccinated in two doses, being the first at one year of age and the second between four and six years of age.

Anti-varicella vaccine comes from attenuated virus, being developed in human diploid cells, derived from the OKA virus (OKAv) strain, which remains latent in sensory ganglia.

VZIG is indicated for varicella or disseminated HZ communicants, those having immunodepression, susceptible pregnant women, newborns (NB) of mothers who had varicella in the last five days before or up to 48 hours after delivery; premature NB with 28 weeks gestation, regardless of mother history of varicella. VZIG provides maximum benefit when early administered after supposed exposure. Expected protection after VZIG administration lasts approximately three weeks. In some situations, one should consider the need for additional vaccination^{13,21}.

Adult vaccination

Anti-HZ vaccine has high doses of attenuated live varicella virus, is well tolerated and has few adverse effects, the most common of which is pain at application site.

Risk factors which may maximize the appearance of PHN are still poorly understood. Some studies indicate that immunosuppression, systemic lupus erythematosus, diabetes and recent local trauma may be associated to higher risk for PHN.

Older age is the only established risk factor for PHN which has been quantified with enough accuracy to justify the vaccination policy²². In 2005, a randomized placebo-controlled study with 38546 adults, has shown that vaccination has decreased the incidence of HZ and PHN in 51.3 and 66.5%, respectively²³. So, vaccination may prevent a disease of low mortality however of high morbidity.

Currently, the Food and Drug Administration (FDA) approves vaccination for adults above 50 years of age.

Vaccines using recombinant glycoproteins are being tested. HZ/su vaccine, which combines glycoprotein E found in the virus causing HZ, with an adjuvant system, AS01B1, intends to improve immune response. A recent study has shown that HZ/su vaccine has significantly decreased HZ risk in adults with 50 years of age or above, having also good efficacy in the population above 70 years of age, which is not true with OKAv vaccine²⁴.

Vaccination is contraindicated for pregnant women, patients with severe immunosuppression and patients with bone marrow or lymph node tumors receiving more than 20mg prednisolone/day¹⁶.

TREATMENT

PHN is a type of chronic neuropathic pain. This is a complex entity involving multiple pathophysiologic phenomena and which, as such, needs to receive a multimodal approach. Studies have shown that no isolated therapeutic approach is effective to control PHN symptoms. In general, combinations of drugs with different action mechanisms are associated to best results²⁵. PHN pain relieve is a challenge and should include drugs, interventionist procedures, a non-pharmacological adjuvant therapies.

Pharmacological treatment

Different drugs may be used to treat PHN, however criteria for the choice of the best analgesic regimen are not well established. A strategy is to

consider patients' profile and pharmacological properties of each group of drugs.

Aiming at orienting the choice of neuropathic pain treatment and, as a consequence, of PHN-associated pain, a classification of available drugs as first, second and third lines was proposed (Table 1).

Table 1. Classification of drugs

| Classification of drugs | Meaning | Action of drugs |
|-------------------------|---|--|
| First line | Efficacy established by different randomized clinical trials | Antidepressants which inhibit norepinephrine and serotonin reuptake Gabapentinoids Lidocaine |
| Second line | Efficacy established by different randomized clinical trials, but there has been questions about the use of the drug with regard to first line drugs based on clinical experience of some authors | Opioids |
| Third line | Efficacy in just one randomized clinical trial or if results of two or more randomized clinical trials were inconsistent | Selective inhibitors of serotonin reuptake Carbamazepine Oxcarbazepine |

It is important to emphasize that the efficacy of different therapeutic options may be shown by means of the analysis of the number needed to treat (NNT) and the number needed to harm (NNH). The ideal is to obtain low NNT and high NNH.

Antidepressants

Tricyclic antidepressants (TAD) and those with dual action have as primary action mechanism the inhibition of norepinephrine and serotonin reuptake in the CNS, this way strengthening the action of descending pain inhibitory pathways. Different international consensus recommend the use of such drugs to treat neuropathic pain and PHN^{26,27}.

Studies indicate that tricyclic antidepressants are effective for PHN, being better than selective inhibitors of serotonin reuptake²⁸. A systematic review published in 2005 has evaluated NNT of amitriptyline, nortriptyline or desipramine to treat PHN and has shown that for 50% pain decrease, NNT has varied from 2.5 to 2.7²⁹, however, adverse effects associated to them may make their use unfeasible. Due to this, TADs should be started in low doses and patients should be monitored for the presence of adverse effects.

Anticonvulsants

Studies involving anticonvulsants have shown that gabapentinoids decrease PHN pain, classifying them as first line drugs to treat this clinical entity. In a Cochrane review, NNT for gabapentin was 7.5 and for pregabalin 3.9³⁰. These data show an advantage for pregabalin as compared to gabapentin, which has been attributed to more linear pharmacological behavior of this substance.

Lidocaine

Topic 5% plaster lidocaine is considered first line drug to treat neuropathic pain in American and European guidelines, and second line drug in Canadian guidelines. In a study comparing lidocaine plaster with pregabalin, there has been decrease in verbal numerical scale (VNS) of 36.3% in the lidocaine group and of 29.8% in the pregabalin group. In addition, lidocaine plaster is better tolerated than pregabalin, contributing to decreased neuronal excitability and pain³¹. It is believed that when applied, lidocaine plaster creates a mechanical barrier which works as a protective element against tactile stimuli, preventing the development of allodynia.

Opioids

Opioids to treat PHN have been object of many discussions. In 2004, the American Academy of Neurology has published a guideline, recognizing

opioids as first line drugs to treat PHN. Other more recent guidelines and published in 2007 and 2010 propose that opioids should be used as second and third line drugs to treat PHN-associated pain. This controversy is reflex of the concern with adverse effects and potential abusive use of opioids. In 2007, Khaliq, Alam and Puri³² have published a randomized clinical trial where they observed that NNT of opioids to treat PHN was 2.7, thus supporting their use to treat this clinical entity.

Other drugs

Topic capsaicin has been proposed to treat PHN for many years, however results obtained after its application in low concentrations are controversial. More recently, capsaicin was formulated as plaster with higher concentration (8%), which seems to have better effects as compared to other compositions. Studies have shown that 8% capsaicin plaster in single applications of 60 minutes is effective to treat PHN patients. In a meta-analysis on 8% capsaicin patch, 196 patients were followed for 12 months. Forty percent of patients had pain intensity decrease equal to or above 30%; 9% had total relief since the second week until the end of follow up^{33,34}.

Analgesic blockades

Pain interventionist procedures during HZ acute phase as a way to prevent PHN in elderly people was studied by Jang et al.³⁵ in a meta-analysis of randomized studies. These authors advocate that affected nerves are inflamed and under effect of sympathetic stimulation which decrease intraneural blood flow with consequent ischemia and irreversible nervous injury. This meta-analysis suggests that interventionist procedures may be effective to prevent PHN when performed during the acute phase of the disease, however sample was small to be conclusive and interventionist procedures were heterogeneous. Further randomized trials are needed to confirm such results.

In a multicenter study performed with 598 patients above 50 years of age and with HZ below dermatome C6, a standard group (antiviral and analgesics) and another standard group associated to single interlaminar epidural with bupivacaine (10 and 80mg) of methylprednisone were compared. The epidural group had better pain decrease at one month follow up, however without long lasting effect and without decreasing the incidence of PHN³⁶. Transforaminal epidural technique guided by radioscopy is an alternative where drug dispersion close to dorsal root ganglion may provide better results.

The efficacy of paravertebral blocks to prevent PHN was studied on 132 acute HZ patients randomized to receive standard treatment (antiviral therapy and analgesics) or standard and paravertebral blocks repeated every 48 hours in a total of 4 interventions. Blockade solution had 10mL of 0.25% bupivacaine and 40mg methylprednisone. After 12 months the incidence of PHN was 2% in the group receiving paravertebral block as compared to 16% in the standard group³⁷.

Botulinum toxin

Botulinum toxin to treat PHN has been proposed. Two double-blind studies have reported its efficacy. In the study of Xiao et al.³⁸ 3 groups of 20 patients were formed: the first for botulinum toxin type A, the second for lidocaine injection and the third for placebo. Patients receiving botulinum toxin in a total of 100 U in serial subcutaneous injections with a distance of 1cm between each application point, had significant pain improvement as compared to patients of the other two groups (p<0.01). Analgesic improvement with botulinum toxin started 3 to 5 days after procedure, with peak of improvement within one week and analgesic effect duration of three months.

In another prospective double-blind study carried out by Apalla et al., 30 PHN patients were evaluated and divided in toxin and placebo groups. The toxin group showed significant pain improvement, with decrease in NVS equal to or above 50% in 4 weeks and in quality of sleep (p<0.001) as compared to the placebo group³⁹.

Kotani et al. have carried out a prospective study with three groups, comparing spinal methylprednisolone (60mg) without preservatives associated to 3% lidocaine, versus spinal 3% pure lidocaine versus no treatment. Participated in the study 270 PHN patients and exclusion criteria were those with trigeminal neuralgia lasting more than one year. Both spinal block groups received four injections at weekly intervals and were

followed for two years. Clinical evaluations and MRI were performed to observe decrease in pain scores and late adverse effect such as arachnoiditis⁴⁰.

Mean pain decrease in the steroid group was 70% being much better than any or drug screening. No significant complications were reported. It is important to emphasize that this study has never been replicated by other investigators and that many considered the protocol risky, especially in the USA, where methylprednisolone packet insert reports risks for spinal administration of this drug.

Radiofrequency

Pulsed radiofrequency (PRF) has been object of randomized study with 96 patients with thoracic PHN, who were divided in two groups: intercostal PRF and control group. PRF was applied once a week in the intercostal nerve of the zone affected by HZ and in segments above and below the injury in a total of three applications. VNS, reduction in tramadol use and quality of life questionnaires were evaluated. The conclusion of this study has revealed that intercostal PRF group had significant improvement of these parameters as compared to control group⁴¹.

Spinal cord stimulation

Spinal cord stimulator (SCS) has been indicated to manage chronic neuropathic pain⁴². A prospective study involving 28 PHN and 4 HZ patients followed by a mean period of 29 months has shown that SCS has promoted significant pain relief in PHN patients, in the proportion of 82%. HZ patients, in turn, had pain remission within two and a half months after SCS installation. These findings suggest that SCS may be a treatment option for PHN intractable pain, contributing to decrease its incidence⁴³.

Implantable pump

Deer et al. have carried out a review study with screenings addressing the use of opioids and non-opioid drugs administered by spinal infusion pump⁴⁴. No study has specifically evaluated PHN.

Deep spinal stimulation

Deep spinal stimulation (DSP) was tested in 22 PHN patients. From these, four had satisfactory response⁴⁵.

CONCLUSION

PHN is associated to complex pathophysiological phenomena and to worsening of quality of life. Its incidence increases with age and its diagnosis is based on clinical data. Prophylactic HZ vaccination may be the best option to prevent it. Antiviral drugs in acute HZ phase do not prevent PHN, but may decrease its severity and duration. Early interventionist procedures may reestablish normal blood flow in the area affected by HZ and cooperate for pain intensity decrease. PHN treatment involves specific drugs for neuropathic 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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