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Postherpetic neuralgia: an update of etiopathogenesis.

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Abstract:

Postherpetic neuralgia (PHN) is defined as a neuropathic pain (NP) that continues from months to years after the cure of the herpes zoster (HZ) infection. The PHN is the main prevalent HZ complication.

The incidence of PHN is 10% in people > 40 years old, 20%-50% of people > 60 years old, and scarcely reported in people < 30 years old and it enhances with increased age and reduced immunity. Consequently, it was mainly reported in the elders. The diagnosis of PHN is relatively straightforward.

The pathophysiology of PHN is poorly understood; different pathophysiologic processes seem to be involved with the development of HZ and PHN. Also, many treatment modalities have been applied to reach maximum efficacy and tolerability. This review article aims to optimize the most recent and the most accepted concepts on the etiopathogenesis of PHN which may help in finding the best lines of management with the most satisfactory outcomes.

Keywords: etiopathogenesis, herpes zoster, postherpetic neuralgia,

Introduction:

Postherpetic neuralgia (PHN) is defined as a neuropathic pain (NP) that continues from months to years after the cure of the herpes zoster (HZ) infection [(1)]. The PHN is the main prevalent HZ complication [(2)]. The incidence of PHN is 10% in people > 40 years old, 20%-50% of people > 60 years old, and scarcely reported in people < 30 years old and it enhances with increased age and reduced immunity. Consequently, it was mainly reported in the elders [(3, 4)].

The diagnosis of PHN is relatively straightforward [(5)]. The history of unilateral cutaneous eruption with blisters in a dermatomal distribution should be presented [(6)]. Continuous pain (burning/lancinating), allodynia, dysesthesias, paresthesias, pruritus, and/or hyperalgesia at or near the site of the cutaneous eruption are the characteristic symptoms of PHN [(5)]. It is well-known that PHN has the potential to impair patients' physical, emotional, and social performance, even leading to psychiatric comorbidities [(7)].

The treatment of PHN is a challenge and should include drugs such as anticonvulsants like pregabalin and gabapentin [(8)], tricyclic antidepressants such as nortriptyline, and amitriptyline [(9)], topical lidocaine, topical capsaicin, opioids, and botulinum toxin [(8)]. The PHN is often resistant to traditional analgesic therapies. Presently, no drug can cure it completely and definitively. The treatment regimens used for relieving PHN give only transient pain relief and some are ineffective at all. Furthermore, these drugs have severe adverse effects and some can result in severe disability to the patients [(10)].

Etiopathogenesis of PHN:

Risk factors of PHN:

The main risk factor for PHN is advanced age. Additionally to the age; the existence of a prodrome symptom (defined as painful and/or abnormal sensations before the onset of the eruption), extensive cutaneous eruption (defined as more than 50 lesions; papules, vesicles, or crusted vesicles), and marked cutaneous pain during the acute HZ infection were considered possible risk factors of PHN [(4)]. A previous meta-analysis also reported that ophthalmic affection, systemic lupus erythematosus, and diabetes mellitus were considered possible risk factors for PHN [(11)].

Pathophysiology of PHN:

The pathophysiological mechanism underlying chronic pain in PHN is still challenging; the exact mechanism of pain in patients with PHN remains unknown and trials to suppose a single unifying hypothesis is indecisive. Different pathophysiologic processes seem to be involved with the development of HZ and PHN [(12)].

In acute HZ, the dormant virus becomes stimulated, replicates, and spreads along the involved neuron, eventually initiating the inflammatory immune responses which can destroy both peripheral and central neurons [(13)].

Damaged peripheral neurons lose the potency to prevent nociception signals of pain. This reduces the threshold for nociceptive pain stimulation and creates spontaneous ectopic discharges. The final outcome produces disproportionate pain with non-painful stimuli (peripheral sensitization) [(14)].

The HZ virus-induced neuronal inflammation also attenuates the descending inhibitory pain pathways, resulting from the dorsal horns compromise (central sensitization) [(14)].

The proximate viral injury leads to continuous excitability of the second-order neurons. Consequently; both normal and enhanced inputs from peripheral nociceptors create increased central responses [(15)]. The peripheral neurons' death and central nervous system (CNS) alternations stimulate an abnormal reorganization of the pain stimuli transmission system with a disorganized innervation aspect that generates the spontaneous pain of PHN [(15)].

On the cellular level; PHN up-regulates the receptors exemplarily linked with pain, like the transient receptor potential vanilloid 1 (TRPV1) [(16)]. Also, there is an enhancement in the proportion of voltage-gated sodium channels and potassium voltage-gated channels [(17)]. These alternations are linked with spontaneous and stimulated pain due to a reduced threshold of action potentials. TPRV1 has been investigated as a non-selective calcium channel with increased calcium permeability that is expressed at the terminal endings of peripheral small-diameter sensory nerves. Therefore, inhibition of the TPRV1 receptor may inhibit the action potential of the peripheral nerves that leads to the transmission of the pain [(18)]. Also, there is evidence of damage of GABAergic inhibitory interneurons at the dorsal horns and loss of descending inhibitions [(16)].

However, there is a preference for the affection of sensory ganglia and nerves; motor compromise may result from the spreading of infection and inflammation to the anterior horn of the spinal cord [(19)]. Several patients presented signs of motor deficits and pain [(20)].

The PHN was divided into irritable nociceptor and deafferentation models [(21)]. The irritable nociceptor model represents serious thermal, mechanical, and tactile allodynia with minimal if any sensory loss and relates with C-fiber stimulation.

Ordinary; the nociceptors of C-fiber are activated by noxious stimuli. Anyway; according to the molecular alternations formerly reported, the C-fibers become

stimulated, reduced their threshold for action potential, and enhance their discharges rate and magnitude, leading to the peripheral nervous system-mediated spontaneous pain and allodynia [(21)].

The deafferentation model was linked with sensory loss and allodynia at the affected dermatome leading to reorganization dorsal horn and reduced number of C-fibers in the involved zone. Also, the skin biopsies obtained in previous research of PHN patients showed a marked loss of free nerve endings in the epidermis of involved sites [(22)].

This phenomenon results in the sprouting of A-β fibers (large-diameter fibers which react to mechanical stimuli such as pressure and touch) and eventually creates connections with the spinothalamic tracts that formerly transmitted pain wherein synapses with C-fibers. This reorganization of the dorsal horn interconnects spinothalamic tracts and pressure-type peripheral stimuli, creating CNS-mediated allodynia [(23)].

Conclusion:

PHN is associated with a complex pathophysiologic mechanism. Consequently, further research is required to permit a more detailed aspect of this serious and disrupting disease and to produce effective treatments for PHN.

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