A Review Of Postherpetic Neuralgia

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Abstract

Postherpetic neuralgia is one of the most feared complications of herpes zoster and one of the most painful conditions seen in pain practice. Both conditions occur much more commonly in elderly patients and immunosuppressed individuals, and stress may be an important instigator of both conditions. Early treatment of herpes zoster may however reduce the incidence of postherpetic neuralgia. Different clinical patterns of postherpetic neuralgia implying different underlying pain mechanisms, may explain the variation in response to treatment but may also lead to more logical choices in management.

ACUTE HERPES ZOSTER INFECTION

Herpes zoster (also known as shingles) is the clinical condition of the reactivation of a latent infection with varicella zoster virus usually contracted after an episode of chickenpox in childhood [1]. The virus tends to be reactivated only once in a lifetime, with the incidence of second attacks being less than 5% [1]. The connection between chickenpox and zoster was first suggested in 1892 by a Viennese physician, Janos Von Bokay, after observing several cases of chickenpox in persons exposed to zoster through household contact [2].

Herpes zoster most commonly affects a single dermatome, is frequently preceded by pain (preherpetic neuralgia) and is defined by the characteristic unilateral vesicular rash confined to that dermatome [3]. Prevalence of the condition is high, with an estimated 500,000 people per year suffering reactivation of the virus in the USA.

Whereas the incidence in immunocompetent patients ranges from 1.2 to 3.4 per 1000 patient years, the incidence in the elderly is considerably higher, ranging from 3.9 to 11.8 per 1000 patient years [3]. This is because T cell immunity to the virus wanes in later life making advanced age the most significant risk factor for the occurrence of reactivated herpes zoster [1]. An additional major risk factor for herpes zoster reactivation is T cell immunosuppression as might occur in conditions such as human immunodeficiency virus (HIV) infection, certain cancers, and immunosuppression treatment after organ transplantation[1,3]. The rash and pain associated with shingles can be both dramatic and severe but in most cases the episode is transient lasting between 2 and 4 weeks [4].

PAINFUL COMPLICATIONS AND THEIR PREVENTION

Although there are several serious complications of zoster (ophthalmic, splanchnic, cerebral, motor), the most common and feared in immunocompetent adults is postherpetic neuralgia (PHN). Its definition is controversial but recent data support the distinction between acute herpetic neuralgia (within 30 days of rash onset), subacute herpetic neuralgia (30-120 days after rash onset), and postherpetic neuralgia (defined as pain lasting at least 120 days from rash onset) [3]. However as PHN may arise at any time after the resolution of acute herpes zoster, a clinically useful definition of PHN is recurrent or persistent localized pain arising or persisting in areas affected by herpes zoster at least 3 months after healing of the skin lesion [5]. The most well established risk factors for PHN are older age, greater severity of acute herpetic neuralgia, more severe rash, and preherpetic neuralgia. Patients with all of these risk factors may have as much as a 50-75% risk of developing PHN [6]. As with other herpes virus infections, psychological distress and stressful life events appear to play an important role in instigating the onset of shingles as well as the development of PHN [3].

In treating the acute phase of herpes zoster, apart from keeping the patient comfortable, an attempt must be made to prevent the development of PHN. The mainstay of acute herpes zoster treatment is oral antiviral therapy and the most commonly used drugs are acyclovir, famciclovir, and

valacyclovir. All of these agents have been shown to promote resolution of skin lesions and reduce the duration of viral shedding and pain [5,7]. Studies have indicated that antiviral treatment started within 48-72 hours of the development of the herpes zoster rash may also decrease the risk of PHN [8]. Antiviral therapy should be provided for patients at extreme risk for developing PHN, including the elderly and individuals with decreased cell-mediated immunity. Many adjunctive therapies are useful in the treatment of acute herpes zoster. Low-dose amitriptyline (25 mg daily) given within 1 month after the onset of zoster for a 90-day course can reduce the risk of PHN by one-half [9]. Corticosteroids added to antiviral therapy have been shown to accelerate healing of skin lesions, reduce analgesic requirement, improve sleep, and promote faster return to normal activity. They do not however affect the incidence of PHN [10]. Although acute pain will be reduced by antiviral and adjunctive drugs, patients will also require analgesics, sometimes strong opioids [6]. Sympathetic and regional blocks with long acting local anesthetics, and local infiltration with local anaesthetic and steroids have also been used to control pain, enhance healing, and prevent permanent nerve damage [11].

POST HERPETIC NEURALGIA FEATURES

PHN is one of the most painful syndromes seen in a pain practice. Its diagnosis is based mainly on the clinical presentation, course, temporal relationship of pain to acute zoster, and the physical examination. The clinical presentation of PHN is variable, and no two individuals experience identical symptoms. Patients may describe their pain as burning, deeply aching, tearing, electric shock–like, lancinating, itching, and/or stabbing. The pain in PHN can be either spontaneous or stimulus-evoked. Some patients also report abnormal sensations in affected dermatomes, including allodynia and/or hyperpathia. Dysaesthesia such as a crawling sensation may also be described. Sensory function may remain intact or may be lost in a dermatomal pattern. Mechanical allodynia to light touch is very common, heat hyperalgesia may be present in some patients, and cold hyperalgesia is rare. Patients may have distinct sensory symptoms and findings, which can coexist in all combinations. Response to therapy also shows significant inhomogeneity. This variability results from damage to a variety of neurological pathways [12].

A link between herpes zoster and the peripheral nerve apparatus was suspected by Bright in 1831, and von Bärensprung identified the dorsal root ganglion (DRG) as the critical structure involved in 1861 [13]. Subsequent pathological studies have demonstrated where and how extensively the nervous system can be damaged by zoster. Pathological changes may include Wallerian degeneration and fibrosis of peripheral nerves, inflammatory infiltration and cystic changes in the DRG, and shrinkage of the dorsal horn [13,14]. There is no evidence however to support a pathological pattern specific to PHN [13].

The complexities of PHN symptomatology as described above, and the variation in response to treatment may imply different underlying pain mechanisms. Three groups of PHN patients have in fact been identified (Table 1). The first two both suffer from spontaneous burning pain and severe mechanical allodynia but differ in their peripheral nociceptor function. Patients in the first group have a relatively mild peripheral nerve injury and the nociceptors in the affected dermatome are sensitized and hyperactive. They experience spontaneous pain and mechanical allodynia in the affected dermatome but demonstrate heat hyperalgesia. These symptoms suggest that peripheral nerves are relatively uninjured and that primary afferent nociceptors in the skin are spontaneously active and pathologically sensitized. Ongoing nociceptor hyperactivity probably produces a prolonged enhancement of responses in spinal cord dorsal horn neurons to afferent stimuli, the so-called central sensitization. Following sensitization, activation of myelinated low threshold mechanoreceptive primary afferents (A? fibers) projecting to the sensitized central nervous system (CNS) neurons, leads to normally non-painful sensations being perceived as painful [3,13,14].

Figure 1

Table 1: Clinical features of PHN subtypes

Subtypes	Sensory deficit	Pain
Sensitized nociceptor burning pain	None	Spontaneous
		Allodynia
Partially deafferented burning pain	Significant thermal	Spontaneous
		Allodynia
Deafferented burning pain	Severe	Spontaneous
		No allodynia

In the second group of patients, there is a significant thermal

sensory deficit within the affected dermatome but the same skin area is extremely painful to light touch. There are two possible explanations for this combination of sensory loss and allodynia. The first is that primary afferent fibres are no longer connected to the skin but continue to be connected centrally. Spontaneously active C fibres could then produce central sensitization as in the first group of patients described above [3,13,14]. A second explanation is that this allodynia is conveyed in uninjured A? fibers that abnormally access spinal cord neurons by anatomically sprouting into upper laminae of the dorsal horn (deafferentation produced central reorganization) [3,13,14]. This idea was supported by histological experiments, however recent publications using animal models of neuropathic pain question the role of sprouting in inducing allodynia [3].

A third group of patients who are a distinct minority have severe sensory loss, pain, but no allodynia. This may be a form of deafferentation pain (anaesthesia dolorosa) caused by hyperactivity of CNS pain transmission neurons and disinhibition of CNS neurons due to loss of pain inhibitory A? fibres [13,14]. It is possible for more than one of the above groups to exist in the same patient. Different zones may have different pain and sensory characteristics, the severity of these characteristics may individually change, and one set of characteristics may evolve into another with the passage of time. This evolution probably represents the effects of slow anatomical CNS reorganization [13,14]. The possibility of multiple mechanisms in the same patient may explain why the response to a single selective intervention is so often partial. Demonstration of the subtype or subtypes present in a patient may lead to a more logical choice of treatments and therefore an improved response. Although research has yet to confirm it, early treatment in PHN may be more effective than later treatment [7].

COMORBIDITIES

Apart from pathophysiological considerations in the management of PHN, the concept of comorbidity is also important in these patients as in all chronic pain patients. Comorbidity is the presence of one or more additional clinically important conditions in a patient that is being treated for a specific disease or dysfunction called the index disease. The most common comorbidities associated with chronic pain are sleep disturbances, depression and anxiety although the relationship among these factors is not straightforward. Despite a scarcity of formal studies directly connecting chronic pain syndromes with sleep interference, depression, and anxiety, it is apparent that PHN can disrupt sleep and possibly mood [15]. In a study of chronic pain sufferers, 82% of participants reported insomnia. Of the subjects who reported sleep disturbances, 60% attributed their sleep problems to pain alone, and 53% indicated that they had never had a problem sleeping before they began experiencing chronic pain [16]. The cause-and-effect relationship between chronic pain and sleep disturbances however cannot be assumed as sleep deprivation studies has suggested that severe sleep disturbances can increase sensitivity to pain [16]. The prevalence of depression in patients with chronic pain is high but although it may seem obvious that someone suffering with a chronic condition would be depressed, it is interesting to compare the prevalence of depression in a chronic pain population with that seen in other chronic, debilitating conditions. In one study, 44% of chronic pain patients were found to have major depression, whereas only 18% of hospitalized severely ill patients demonstrated symptoms of depression [17]. As in patients with sleep deprivation, it is unclear whether chronic pain leads to depression or whether depression causes an increased sensitivity to pain. Both a depressed mood and anxiety can lead to an increase in the intensity of pain perceived by the patient [18]. Pain, sleep disturbance, and mood disorders cause functional impairment in many areas of life, including an inability to concentrate, loss of employment, and a decrease in social and other activities [19]. Furthermore the coexistence of these comorbidities in a patient has important implications for management because it may be difficult to accurately assess the index disease, resulting in treatment not producing the expected outcome [20]. Therefore, before treatment is commenced it is important to adequately characterize the PHN syndrome for the particular patient, and given the subjective nature of the condition, baseline measurements of pain character and intensity should be measured in order to assess the effectiveness of treatment. Baseline quality of life measurements should also be included and this can be done with a daily pain diary that includes measures of spontaneous and evoked pain, sleep disturbance and general well being.

TREATMENT OPTIONS

Benefits of pharmacotherapy for improving quality of life, including physical and emotional function, have been found less consistently than for reducing pain intensity [21]. Drug related side effects are common, not only because of the nature of the drugs used but also because many patients with this condition are older, take other medications and have co-

morbid illnesses [21].

Topical lignocaine as a 5% patch provides effective treatment with minimal side effects. Lignocaine diminishes ectopic discharges within superficial sensory afferents by blocking sodium channels, and so would be of greatest benefit in areas with intact peripheral nerve function rather than in areas with sensory loss. However although lignocaine itself has no antiallodynic effect, the patch itself serves as a mechanical barrier between skin and clothing in patients with allodynia. Systemic side effects are unlikely because the patch results in clinically insignificant serum lignocaine levels, even with chronic use [12,22].

Anticonvulsants and in particular gabapentin are useful treatments in many chronic neuropathic pain syndromes. Gabapentin in doses of up to 3600mg per day significantly reduced pain compared with placebo and some trials have also demonstrated improvements in sleep, mood, and quality of life. Side effects include somnolence, dizziness, cognitive impairment, and exacerbation of gait and balance problems. These as well as renal impairment may require dosage adjustment [21].

Tricyclic antidepressants such as amitriptyline, nortriptyline, and desipramine have been found useful in central post-stroke pain and can be effective adjuncts in reducing the neuropathic pain of PHN. The clinical literature supports a high response rate, generally at least 50% [23]. These agents inhibit the reuptake of norepinephrine and serotonin, which act on descending pathways between the brain stem and the dorsal horn of the spinal cord [4]. They may be more useful in the deafferentation type of PHN. The difficulty with these drugs is their adverse side-effect profile and they must be used cautiously in patients with cardiovascular disease, glaucoma, urinary retention and autonomic neuropathy. Nortriptyline and desipramine have fewer side effects and are better tolerated than amitriptyline [21]. It has been suggested that tricyclics should be used to treat constant pain and that anticonvulsants should be used for lancinating pain, but trials have shown no evidence of a differential treatment response [21].

There is a large body of evidence indicating that excitatory amino acids acting at N-methyl-D-aspartate (NMDA) receptors, cause the spinal hyperexcitability in neuropathic pain states that is responsible for the symptoms of spontaneous pain and allodynia [24]. There is clinical evidence that NMDA blockers reduce pain caused by nerve injury. One such non-competitive NMDA receptor blocker is the phencyclidine derivative ketamine. Significant reduction in pain intensity has been demonstrated in patients with PHN with subcutaneous infusion of ketamine lasting several days [25].

The severity of pain however returned to pre-treatment levels after termination of the infusion. In addition, several side effects such as painful induration of the injection site, dizziness, fatigue and psychomimetic side effects make its use a major problem. The antiviral and antiparkinsonian drug amantadine has also been shown to be an NMDA receptor antagonist. A report of three patients with chronic neuropathic pain, demonstrated that the response to acute treatment with intravenous amantadine far outlasted the duration of the drug's administration, and resulted in complete or near complete resolution of pain, without side effects [26]. Magnesium ions have been shown to exert a physiological block of the ion channel associated with the NMDA receptor. It is possible that magnesium chloride infusion at the appropriate dose may be useful in neuropathic pain although this has not as yet been demonstrated [24].

Opioids suppress the central response nociceptor input and primary afferent nociceptors have opioid receptors on their central terminals. Thus opioids should be most useful when PHN pain is maintained by input from dysfunctional afferents [12].

This is probably why patients with central post-stroke pain have been shown not to improve with opioid medication [21]. Controlled release oxycodone and morphine have been shown to significantly improve pain and sleep disturbance in PHN but not physical function and mood [21]. Constipation, sedation and nausea are the most common side effects and the most common reasons for withdrawal. Elderly patients may also have problems with cognitive impairment and mobility that may lead to an increased risk of hip fracture [21]. Tolerance to side effects usually occurs with the exception of constipation.

In the presence of nerve injury and tissue inflammation, the sympathetic nervoussystem may mediate pain after abnormal chemical and anatomical coupling between sympathetic postganglionic and sensory neurons [27]. Sympathetic nerve blocks have been used in the treatment of PHN and have two therapeutic goals: pain relief in patients with PHN, and prevention of PHN by treating patients with acute herpes zoster. The risk factors for PHN that have been identified include acute pain severity and rash severity. For this reason any intervention which decreases pain, inflammation, and

nerve damage during the acute phase of herpes zoster may be expected to lessen the likelihood of PHN developing. This issue however remains controversial because the available data has methodological flaws making interpretation difficult. Trials demonstrating the effectiveness of non-invasive preventative treatments for PHN such as topical lignocaine, antidepressants and anticonvulsants, may render the controversy obsolete [27]. Once PHN has become established, sympathetic nerve blocks do not appear to provide prolonged relief. This poor response of sympathetic blockade in PHN suggests that the sympathetic nervous system plays only a limited role in accounting for pain and allodynia in PHN [27]. On

the other hand, sympathetic nerve blocks do provide considerable relief in acute herpes zoster.

Other treatment options for PHN include cognitive behavioural therapy methods incorporating relaxation techniques. These should always be considered in conjunction with other forms of treatment in view of the complex nature of PHN and the psychological factors that may exacerbate but also be exacerbated by this often severe and chronic disease [11]. Invasive methods such as implanted spinal cord dorsal column stimulators, and implanted spinal catheters and pumps may provide pain control in patients who have severe pain not controlled by any other form of therapy [11]. Neuroablative procedures such as dorsal root entry zone lesion (DREZ) may prove useful in hopeless cases that show no response to any other therapy, although following this some patients may have recurrence of pain in addition to having developed sensory loss in the affected area [11].

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