Postherpetic neuralgia

How to prevent it, how to treat it

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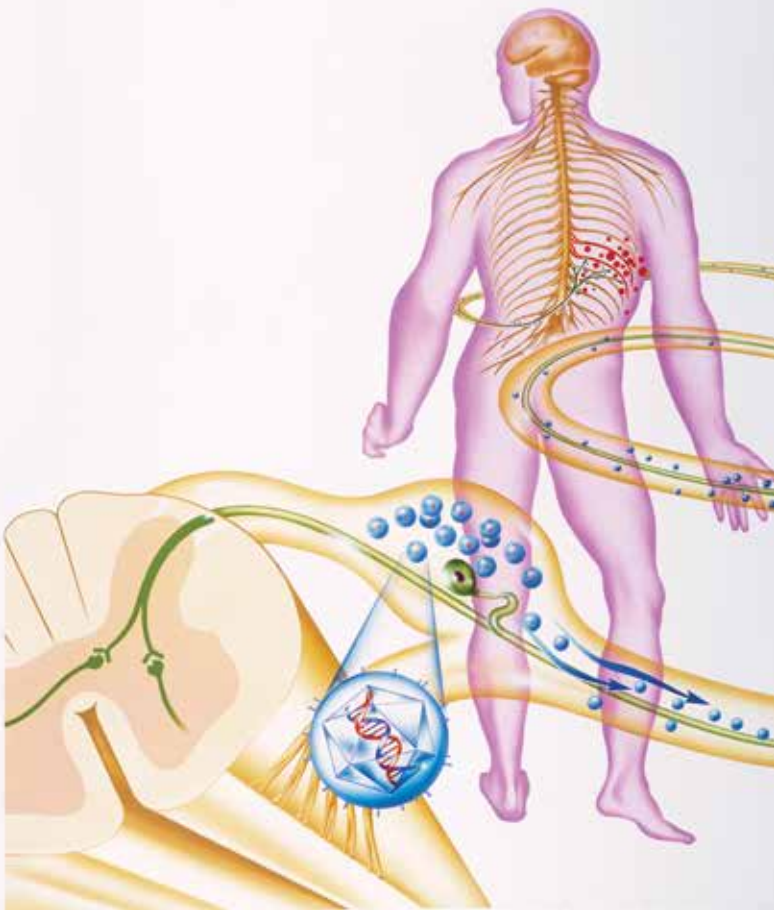
Postherpetic neuralgia (PHN) is a common late complication of acute shingles. This neuropathic pain is often severe and accompanied by sensitivity to touch. It significantly impairs the quality of life of affected patients. The difficulties in treating PHN justify preventive measures such as vaccination and early aggressive management of the acute shingles episode.



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KEY POINTS

- Shingles, resulting from reactivation of varicella-zoster virus (VZV; the cause of chickenpox) is a common acute disease, particularly in elderly and immunocompromised patients.
- The shingles rash is accompanied with, or may be preceded by, acute, often severe pain; the persistence of neuropathic pain beyond three months is described as postherpetic neuralgia (PHN).
- PHN occurs more often in the elderly and has significant negative effects on quality of life.
- Vaccination with attenuated VZV is a preventive strategy reducing incidence of acute shingles and thereby PHN; it is recommended for patients over 60 years and will be funded for patients over 70 years from November 2016.
- Treatment of PHN should follow established guidelines for neuropathic pain; in view of the localised pain and the typically elderly and frail patients affected, topical lignocaine 5% patch is a specific first-line treatment option.
- Systemic first-line treatments include pregabalin, gabapentin, tricyclic antidepressants and serotonin-noradrenaline reuptake inhibitors, with tramadol second-line and conventional opioids third-line options.

Varicella-zoster virus (VZV) is an exclusively human neurotropic alphaherpesvirus that invokes cellular-mediated immunity in patients who develop the primary infection varicella (chickenpox). The virus remains dormant in the cranial nerve ganglia, dorsal root ganglia and autonomic ganglia along the neuraxis for years after the initial infection. Reactivation of latent VZV in such infected neural ganglia produces dematomal skin lesions called herpes zoster or shingles (Figure).[1] Such reactivation occurs when cellular immunity declines – i.e. with increasing age, with some diseases (e.g. malignancy or HIV infection) or when patients are on certain treatments such as chemotherapy, immunosuppressants or corticosteroids.[1] Complete resolution of symptoms occurs in two to four weeks in many patients.[2] However, some patients may continue to suffer from prolonged sequelae of shingles

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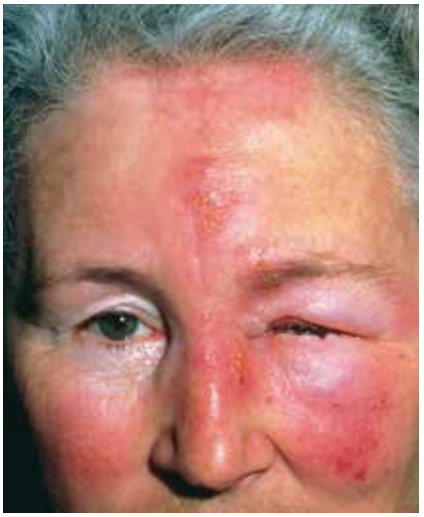

Figure. Elderly woman with shingles affecting the trigeminal nerve.

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that include, most often, postherpetic neuralgia (PHN) and, rarely, neurological disorders including ophthalmoplegia, multiple cranial nerve palsy, vasculopathy, myelopathy, motor deficits (often subtle) and various inflammatory disorders of the eye.[3]

Although shingles itself is a painful condition (pain occurs in 80% of affected patients and is often a prodromal symptom), PHN is often defined as a 'clinically meaningful pain' persisting more than three months after the infection.[4]

Epidemiology of shingles and PHN

The overall estimated lifetime risk of shingles is about 30%, with more than two-thirds of cases occurring in those aged over 50 years. In Australia, approximately 150,000 new cases occur each year (an incidence of about 7/1000 people/year), representing around 0.1% of all GP visits. Subsequent episodes of shingles are rare (occurring in fewer than 5% of individuals) but more likely to occur in patients who are immunocompromised.

Subsequent development of PHN also increases with age, with a reported incidence of 18% in those aged 50 years, and over 30% in those aged 80 years; 80% of cases of PHN occur in patients older than 50 years.[1]

Burden of disease

Chronic neuropathic pain conditions are perceived as being more severe than other types of chronic pain and associated with greater impairment of health-related quality of life, patients' daily functions and, in particular, sleep. These general findings have been confirmed for PHN specifically.[4] The amount of time off work, loss of productivity and presence of associated comorbidities such as anxiety, depression and sleep disorders exacerbate the economic burden and psychosocial dysfunctions of neuropathic pain.[5]

Clinical presentation

In more than half of all cases of shingles, herpes zoster-associated pain precedes the rash and vesicular eruption by up to seven days. This is often perceived as unilateral, dermatomal, spontaneous, burning pain and paraesthesia, accompanied by itching with varying symptom severity in the affected dermatome.

Clinically subtle presentations of VZV reactivation with the main symptom of unilateral dermatomal pain without skin eruptions are called zoster sine herpete. There are also reports of neurological dysfunction without skin lesions or rash.

Whereas acute herpes zoster-associated pain has features of inflammatory and neuropathic pain, PHN is a purely neuropathic pain condition. Three main characteristic features are described by patients with PHN:

- a constant deep aching or burning pain commonly perceived over the affected dermatome
- severe paroxysmal, lancinating pain that shears through the area with varying interval and duration
- persistent mechanical and/or cold allodynia, which is particularly disturbing to most patients, causing distress on slight tactile contact (clothes, blankets) or even airflow (draught).[6]

In addition to such 'positive' symptoms, most patients have some 'negative' symptoms such as reduced sensation (hypoaesthesia) or even numbness.

The neuropathic pain of PHN progressively increases throughout the day and persists through the night; this variation appears unaffected by treatment and may be related to diurnal neurohormonal and neurophysiological changes.[7]

Diagnosis

Neuropathic pain is defined as 'pain initiated or caused by a primary lesion or disease of the somatosensory system'.[8] For research purposes, pain mapping, quantitative sensory testing (QST), the capsaicin response test and skin biopsies have been used to study the course of illness and correlation with pain symptoms. QST identifies mechanical allodynia with the use of foam, cotton wool or a soft paintbrush and thermal allodynia with warmth, cold and heat pain detection.[9]

The diagnostic criteria for PHN are:

- pain persisting or recurring more than three months after the onset of herpes zoster infection
- a painful dermatomal lesion
- a preceding herpetic eruption in the same territory, and
- pain preceding the eruption by fewer than seven days.

Additionally, neuropathic pain inventories such as the painDETECT questionnaire that systematically evaluate the clinical symptoms of neuropathic pain described above can be used to screen for neuropathic pain.[10] Other questionnaires that require a short examination such as the Leeds Assessment of Neuropathic Symptoms and Signs Scale (LANSS) or the Douleur Neuropathique 4 questions (DN4) can also be used.[11]

Risk factors for developing PHN

Being aware of the risk factors for developing severe PHN can be helpful to the GP in stratifying a patient's symptoms on initial presentation and the presence of these may justify the use of more aggressive treatment to try to prevent PHN.

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Certain clinical features of acute shingles, including prodromal pain, severe acute pain, severe rash and ophthalmic involvement, more than double the risk of developing PHN.[12] Other predictive factors are older age, being immunocompromised, being in a lower income group and not receiving antiviral treatments.[13]

As chronic pain is a biopsychosocial phenomenon, it is not surprising that greater anxiety and depression, lower life satisfaction and greater disease conviction are psychological determinants for PHN.[14,15]

Preventive strategies for PHN

Vaccination

A vaccine containing approximately 14 times more live attenuated VZV than that in varicella (chickenpox) vaccines has shown efficacy in reducing the incidence of acute shingles by 51%[16] and thereby the incidence of PHN by 67%,[17] although this is not beyond its effect on suppressing acute episodes.[18] The estimated number-needed-to-vaccinate to prevent one case of acute shingles has been shown to be 11 (95% confidence interval [CI], 10–13) and for PHN, 43 (95% CI, 33–53).[19]

In view of these excellent results, the National Centre for Immunisation Research and Surveillance (NCIRS) recommends a single vaccination for adults aged 60 years and over who are not immunocompromised.[20] People with asymptomatic HIV infection or those anticipating alteration of their immunity (e.g. due to future immunosuppressive therapy) can be vaccinated on a case-by-case basis. These recommendations are in line with those made by the Advisory Committee for Immunization Practices of the US Centers for Disease Control and Prevention.[21]

From November 2016, zoster vaccine will be funded for all adults at 70 years of age as part of a National Shingles Vaccination Program (NSVP) in Australia; a single catch-up dose will also be funded for adults aged 71 to 79 years for a five-year period.[20]

Treatment of acute shingles

Antiviral agents started within 72 hours of rash onset provide accelerated resolution of skin lesions and reduce acute pain caused by shingles but, regrettably, have no preventive effect for PHN.[22] Famciclovir or valaciclovir are preferred over aciclovir, as they confer similar benefits but have a better pharmacokinetic profile and fewer adverse effects.[23,24]

Multimodal oral analgesia should be used to treat acute shingles pain and may therefore be a potential approach to preventing PHN; however, the evidence for such an effect is limited.[25] Prospective studies have indicated that regular use of paracetamol and tramadol or oxycodone is effective.[23] Topical lignocaine (in the form of patches) and topical aspirin have some support for use in treating the pain of acute shingles,[26,27] whereas data on corticosteroids and anticonvulsants (gabapentin and pregabalin) are contradictory.[28-30] Early use of the tricyclic antidepressant (TCA) amitriptyline during acute shingles for three months after diagnosis has been shown to reduce PHN prevalence by more than one-half at six months.[31]

Epidural corticosteroid injections have been used with some success in the treatment of pain caused by acute shingles, but have shown only limited benefit in the prevention of PHN and are not recommended as a routine treatment.[25]

Pharmacological treatment of PHN

The pharmacological treatment of neuropathic pain in general has an excellent evidence base with recently published recommendations by the Special Interest Group on Neuropathic Pain (NeuPSIG) of the International Association for the Study of Pain (IASP).[32]

In some instances these otherwise more general guidelines address PHN specifically, recommending topical lignocaine 5% patches as a possible first-line option in view of the localised pain and when patients are elderly and frail. Often the age

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and frailty of patients preclude the use of systemic first-line treatments discussed below due to concerns of increased adverse effects in this group. In PHN specifically, lignocaine patches have shown superior efficacy to pregabalin with significantly lower rates of adverse effects.[33] However, in patients unresponsive to such monotherapy, the addition of pregabalin increased efficacy.[34]

For neuropathic pain in general, the guidelines recommend the alpha-2-delta modulators pregabalin and gabapentin, TCAs (off-label use) and the serotonin and noradrenaline reuptake inhibitors (SNRIs) duloxetine (indicated specifically for diabetic peripheral neuropathy) or venlafaxine (off-label use) as first-line treatment options. PHN-specific evidence is lacking for the SNRIs, but plentiful for the other first-line treatments.

High-dose topical capsaicin (8%) patches and tramadol are recommended as second-line treatment options. Capsaicin patches are approved for PHN treatment by the US Food and Drug Administration, but currently not available in Australia.

Although opioids are highly effective in neuropathic pain, they are only regarded as third-line treatment due to specific problems with their long-term use (i.e. tolerance, dependence, abuse, diversion and endocrine effects),[32] and their lack of efficacy in improving physical functioning in patients with neuropathic pain.[35] The current exception is tramadol, which, as noted above, is rated by the guidelines as second-line treatment. Tramadol shows excellent efficacy in neuropathic pain, partially due to its inhibitory effect on noradrenaline and serotonin reuptake as well as reduced risks compared with conventional opioids. A future option may be tapentadol, although studies are currently limited to diabetic polyneuropathy and neuropathic back pain.[36]

Due to the current weak quality of evidence in supporting botulinum toxin A, this therapy has also been rated as a third-line treatment (off-label use). Although there has been a positive trial of subcutaneous injections of botulinum toxin A in PHN, it is recommended only in refractory cases.[37]

The evidence for the efficacy of a number of medications that are still used in neuropathic pain states including PHN have been rated as being inconclusive by the guidelines; these include carbamazepine, oxcarbazepine, topiramate, lamotrigine, selective serotonin reuptake inhibitor antidepressants, topical clonidine and low-concentration capsaicin cream.[32] Data on combination therapy have also been rated generally as inconclusive, although the combinations of pregabalin or gabapentin with duloxetine or TCAs specifically are mentioned in the guidelines as an alternative to increasing doses of monotherapy.[32] Similarly, as outlined above, the combination of topical lignocaine 5% patches with systemic first-line treatments can be considered, particularly in frail patients.[38]

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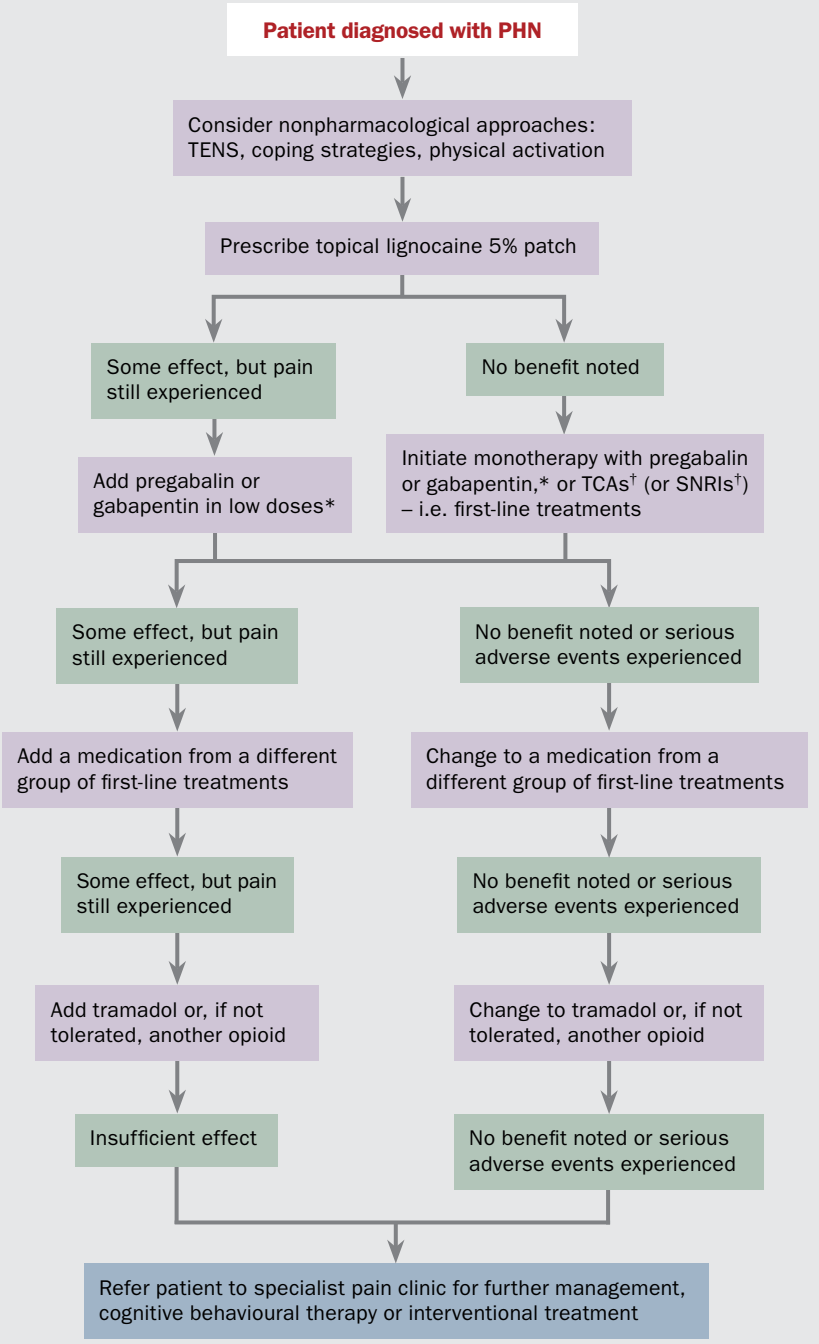
AN APPROACH TO POSTHERPETIC NEURALGIA TREATMENT[39]



Abbreviations: PHN = postherpetic neuralgia; SNRIs = serotonin-noradrenaline reuptake inhibitors; TCAs = tricyclic antidepressants; TENS = transcutaneous electrical nerve stimulation.

* Pregabalin is preferable over gabapentin due to the better pharmacokinetics (longer half-life and higher, more reliable and dose-dependent oral bioavailability) and – in the Australian context – being funded by the PBS.
† Off-label use.

Modified from: Gilron I, Watson CP, Cahill CM, Moulin DE. Neuropathic pain: a practical guide for the clinician. CMAJ 2006: 175: 265-275.[39]

The guidelines provide weak recommendations against the use of cannabinoids and sodium valproate and strong recommendations against the use of levetiracetam and mexiletine in neuropathic pain.[32]

A suggested approach to the treatment of patients with PHN based on current evidence and guidelines is given in the flowchart.

Conclusion

Acute shingles is common in elderly people and may result in chronic PHN, a severe and debilitating neuropathic pain condition. A preventive strategy is vaccination with the attenuated virus. Treatment of PHN should follow established guidelines for the treatment of neuropathic pain, with topical lignocaine 5% patches a specific localised option that has minimal adverse effects in elderly patients, who are most often affected by PHN. MT

References

A list of references is included in the website version of this article (www.medicinetoday.com.au).

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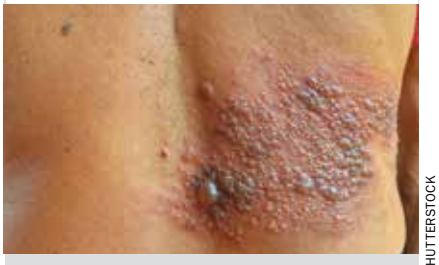
ONLINE CPD JOURNAL PROGRAM

List the three main characteristic features of the pain described by patients with postherpetic neuralgia.



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