

Welcome to the fourth issue of Challenges in Neuropathic Pain, a newsletter brought to you by the members of the Multidisciplinary Panel on Neuropathic Pain. This issue presents the second in a series of treatment recommendations for neuropathic pain. The recommendations aim to provide Hong Kong clinicians with up-to-date information on treatment strategies and assist in everyday clinical practice. Our regular features, including a literature review, Q&A, useful Web sites and a calendar of upcoming conferences, will keep Hong Kong clinicians informed of the latest news on neuropathic pain.



Multidisciplinary Panel on
Neuropathic Pain

神經痛跨學科研究小組

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RECOMMENDATIONS FOR THE MANAGEMENT OF POSTHERPETIC NEURALGIA

One of the key initiatives of the Multidisciplinary Panel on Neuropathic Pain is the development of treatment recommendations for a number of common neuropathic pain syndromes. This will better assist general practitioners to recognize the signs and symptoms of neuropathic pain and initiate appropriate treatment. The recommendations will also provide guidance on when to refer patients to specialists. This issue features a summary of the recommendations for managing postherpetic neuralgia (PHN). The project leader for developing these recommendations was Dr PP Chen.



Pathophysiology and Prevalence

Postherpetic neuralgia is a neuropathic pain syndrome that occurs following acute herpes zoster infection, or shingles. Herpes zoster infection is caused by reactivation of the chicken pox virus (varicella zoster) that can lie dormant in the sensory nerve roots of the spinal cord. Virus reactivation may be associated with waning cellular immunity caused either by age-related immune system dysfunction or immunosuppression.¹ Herpes zoster lesions typically erupt in the thoracic, cervical and ophthalmic dermatomes. Varicella zoster, or chicken pox virus, can damage the primary sensory neuron, including the dorsal root ganglion, which can lead to PHN. Peripheral and central pathophysiological mechanisms have been identified or proposed.

PHN is usually defined as pain persisting for more than 3 months after herpes zoster skin lesions have healed. PHN is often difficult to treat and may last many years. Patients with PHN may develop physical and social disabilities, as well as psychological distress.^{2,3}

The reported incidence of PHN after acute herpes zoster infection varies from 9%-34%.⁴ The risk of PHN increases sharply with age, with up to 50% of affected patients being older than 60 years and 75% older than 70 years.^{5,6} The risk factors for PHN are outlined in Figure 1.

Antiviral treatment of acute herpes zoster (with famciclovir, valacyclovir or acyclovir) may reduce the overall duration of pain and risk of developing PHN.^{7,8} Corticosteroids have been used prophylactically by some clinicians, but there is little evidence to support their use. Prophylactic treatment with low-dose amitriptyline in patients older than 60 years may reduce the incidence of PHN by more than 50%.⁹

Diagnosis

PHN is diagnosed on the findings of a complete medical history and physical examination, as summarized in Figure 2.

Patients with PHN can present with different symptom patterns. Some patients

Figure 1: Risk factors for PHN^{1,4,6}

- Old age
- Severe, acute pain during acute herpes zoster infection
- Severe skin eruption or rash during acute herpes zoster infection
- Sensory dysfunction in the affected dermatome during acute herpes zoster infection
- Pain before the appearance of the rash

Figure 2: Diagnostic, clinical features of PHN

- Pain localized to the dermatome affected by the herpes zoster rash
- Pain described as burning and/or throbbing, or sharp and shooting
- Allodynia
- Pain accompanying movement
- Areas of scarring or hypopigmentation caused by the herpes zoster rash
- Presence of psychosocial distress

have marked allodynia with minimal sensory deficits, while others have minimal allodynia but substantial sensory loss. The pathological mechanisms behind these changes can be very complex and several approaches are often needed to manage PHN successfully.

Recommended Management of PHN

The pharmacological treatments included in these recommendations are based on published clinical evidence in PHN patients and current clinical practice. However, some agents may not be approved for use in neuropathic pain syndromes. Full prescribing information should be consulted before initiating drug therapy.

The mainstay treatments for PHN include tricyclic antidepressants (TCAs) and anticonvulsants (Figure 3).¹⁰⁻¹³ Topical lignocaine administered via a patch also effectively treats PHN, and provides an alternative choice for patients who experience systemic side effects from other therapies.¹⁴⁻¹⁶ In addition, recent evidence suggests a possible role for oral opioid analgesics in the management of PHN.¹⁷ Physical therapy, eg, transcutaneous electrical nerve stimulation (TENS), may be a useful adjunct, although there is no strong evidence for its effectiveness in PHN.

“The mainstay treatments for PHN include tricyclic antidepressants and anticonvulsants”

Patients remaining unresponsive to first-line therapies after 8 weeks should be referred to a pain medicine specialist. With these patients, a multidisciplinary approach to treatment, involving a pain management physician, clinical psychologist and other allied health professionals, is often appropriate.

General Management

1. Conduct a careful medical and psychosocial evaluation.
2. Set a realistic expectation for the treatment.
3. Educate the patient on the disease and treatment side effects.
4. Provide psychosocial counselling if necessary, taking into account the chronic nature of this pain syndrome. Counselling is intended to reduce influencing psychosocial factors that may affect the pain and to prevent the development of pain behaviours.

Specific PHN Treatments

1. TCAs are effective in treating PHN and are often used as first-line therapy.^{5,10,11} However, the most widely used TCA, amitriptyline, is associated with significant adverse effects, including sedation, anticholinergic effects and postural hypotension. Nortriptyline is as effective as amitriptyline and has a more favourable adverse event profile.¹⁸

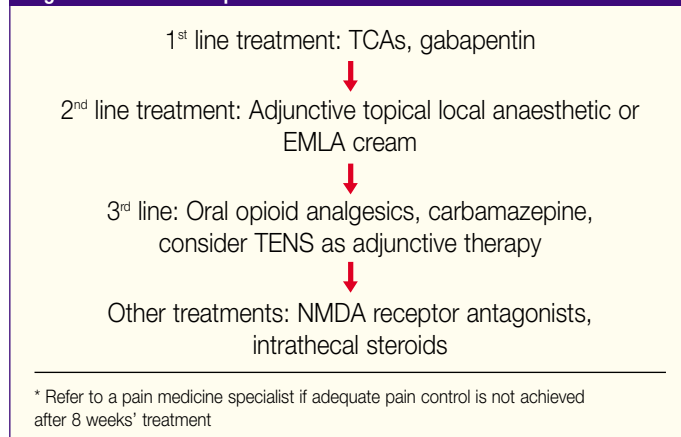
Dosing schedule: Start low-dose amitriptyline or nortriptyline therapy (10-25 mg at night) and titrate weekly up to the maximum tolerated dose, or a maximum dose of 150 mg.

2. Two large, placebo-controlled, randomized trials have indicated that gabapentin is a useful alternative to amitriptyline, with similar efficacy, but fewer associated side effects.^{12,13} For patients older than 60 years, or in cases where TCAs are not tolerated or are contraindicated, gabapentin may be used. In some practices, gabapentin is considered the first-line therapy for PHN.

Dosing schedule: Gabapentin should be commenced at 300 mg at bedtime and increased by 300 mg, every 3 days, up to a dose of 1,800 mg daily (given in 3 divided doses). If higher daily doses are required for maintenance, the maximum recommended dose is 3,600 mg daily. For elderly patients or patients susceptible to side effects, it is recommended to increase gabapentin dosage by 300 mg every week, or to commence with a lower dose (eg, 100 mg).

3. Add a topical local anaesthetic, such as a lignocaine patch or EMLA (Eutectic Mixture of Local Anaesthetic) cream. This can be first-line treatment if antidepressants and anticonvulsants are contraindicated.
4. Carbamazepine is commonly used to treat PHN, but there is little evidence to support its use in this neuropathic pain condition.
5. Consider tramadol or opioids if antidepressants and anticonvulsants are ineffective or are contraindicated.
6. Consider TENS as adjunctive therapy.
7. If adequate pain control is not achieved after 8 weeks, consider referring the patient to a pain medicine specialist for alternative therapies, such as N-methyl D-aspartate (NMDA) receptor antagonists or intrathecal steroids. A multidisciplinary approach in managing these difficult-to-treat patients may be necessary.

Figure 3: Treatment options for PHN*



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CASE PRESENTATION

In each issue, a case study is presented on a relevant neuropathic pain syndrome. Reviewing case studies will help to improve your diagnostic approach to neuropathic pain and increase your understanding of how to select treatment strategies based on presenting symptoms. In this issue, a case of poststroke pain is discussed. Poststroke pain may also be referred to as thalamic syndrome or Dejerine-Roussy syndrome.

Poststroke Pain

Presenting Symptoms

A female aged 57 years presented to the Accident and Emergency department of a local hospital with sudden onset of pain and paresthesia on the right side of her body.

Medical History

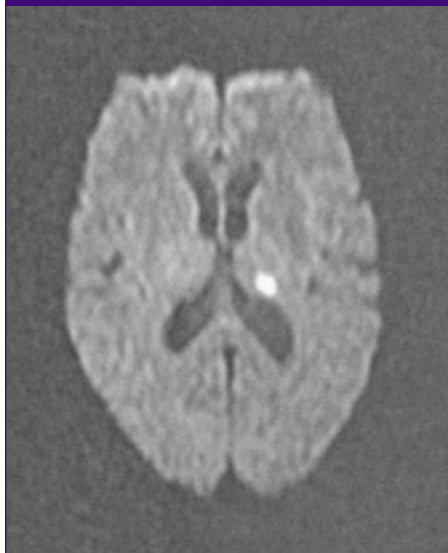
The patient had recently been diagnosed with diabetes mellitus and took metformin 500 mg bid. She was a non-smoker and had no history of hypertension, ischaemic heart disease or cardiac arrhythmia.

Clinical Examination

During examination, reflexes and plantar responses were normal. Pinprick, light touch and proprioception sensations were intact. The patient's blood pressure was 136/72 mmHg, and an electrocardiogram showed normal heart rhythm and no signs of ischaemia. A computed tomography (CT) scan of the brain did not show any abnormality. A diffusion-weighted magnetic resonance imaging (MRI) scan of the brain was performed on the following day; MRI can identify cerebral infarcts within minutes of onset. The CT and MRI scans were performed within 3 days of symptom onset. The MRI revealed an acute infarct in the left lateral thalamus (Figure 4).

The patient was treated with aspirin and discharged. However, her pain intensified over the next few weeks. Amitriptyline (25 mg tds) was prescribed, but the patient failed to respond after 4 weeks' treatment. She switched to gabapentin (300 mg tds) with good results.

Figure 4: MRI scan of the brain revealing a left lateral thalamic infarct



Interpretation

Lateral thalamic infarct is a common cause of stroke, accounting for about 15% of lacunar infarcts. Ventrolateral thalamus infarcts were first described more than 100 years ago. The ventrolateral nuclei are supplied by the thalamogeniculate arteries, which usually arise from the posterior cerebral arteries. Occlusion of the thalamogeniculate arteries can cause 3 different clinical syndromes:

1. *Pure sensory stroke* due to a small infarct of the thalamic somatosensory nuclei.
2. *Sensorimotor stroke*, in which the sensory nuclei and the posterior limb of the internal capsule are involved.
3. *Large thalamic stroke*, which produces hemisensory symptoms, hemiataxia and hemichorea.

Pure sensory stroke usually manifests as paresthesia in the face, neck, trunk and limbs. Sensory loss, if any, is usually minimal. Pain rarely develops immediately after the stroke, but does develop after weeks or months.

Management

Nociceptive pain, such as frozen shoulder, should be treated with analgesic agents (eg, non-steroidal anti-inflammatory drugs [NSAIDs] and opioids), intracapsular injection and physiotherapy. Severe, central, poststroke pain can be treated with amitriptyline and/or gabapentin. Other treatments, such as lamotrigine or adjunctive use of mexiletine, may also be effective.

Q&A

Readers are encouraged to send questions to members of the Multidisciplinary Panel on Neuropathic Pain. Please forward your questions concerning any aspect of neuropathic pain and its management to mpnp@medimedia.com.hk or fax to (+852) 2559 6910.

Can vitamin B and multivitamin supplements be used to treat neuropathic pain?

When this question was asked to Panel members, most indicated that they had little experience or knowledge of the effectiveness of vitamin B or multivitamin supplements in treating neuropathic pain. Vitamin deficiency (eg, thiamine, pyridoxine and vitamin B₁₂) can cause polyneuropathy, which may be painful. Some studies have indicated that the vitamin B₁₂ derivative, methylcobalamin, may have a small effect on nerve regeneration (Yamazaki, et al. *Neurosci Lett* 1994;170:195-197). In the clinical setting, one of the Panel members indicated that they had not found vitamins effective in treating neuropathic pain. However, in an African study, supplementation with the vitamins thiamine or pyridoxine was associated with improved diabetic peripheral neuropathy symptoms (Abbas ZG, Swai AB. *East Afr Med J* 1997;74:803-808). A balanced diet with vitamin supplementation, if necessary, is important for patients with neuropathic pain and, possibly, to prevent progression of neuropathy. However, vitamins should only be used as an adjunct to medical treatment of neuropathic pain.

LITERATURE REVIEW

Backonja M, Glanzman RL. Gabapentin dosing for neuropathic pain: evidence from randomized, placebo-controlled clinical trials. Clin Ther 2003;25:81-104.

The aim of this paper was to review data on the efficacy and tolerability of gabapentin in the treatment of neuropathic pain in adults, and to determine the optimal dosing schedule. The authors reviewed data from 5 randomized, placebo-controlled trials with gabapentin, 4 of which have been published. They also summarized other currently available treatments for neuropathic pain: NSAIDs, opiates, TCAs and other anticonvulsant drugs, including carbamazepine, phenytoin and lamotrigine.

Of the reviewed gabapentin trials, 2 were in patients with diabetic neuropathy, 2 were in patients with postherpetic neuralgia and 1 was in mixed neuropathic pain syndromes. The authors found that gabapentin was effective in treating all of these conditions, reducing symptoms such as allodynia, burning pain, shooting pain and hyperesthesia. Adverse effects were mostly mild to moderate in nature and tended to diminish over time. On the basis of the clinical review, the authors provided a recommended dosing schedule for gabapentin. Patients should be started on gabapentin 300 mg/day and titrated to 900 mg/day by day 3. Within 2 weeks of initiating treatment, the dose should be titrated to achieve optimal efficacy (900 to 1,800 mg/day). The maintenance dose (1,800 to 3,600 mg/day) should be based on the patient's response to therapy.

WEB SITES ON NEUROPATHIC PAIN

Various Web sites are devoted to neuropathic pain or pain management. Most of these are not based in the Asia-Pacific region but, nevertheless, provide useful information on pain for clinicians and patients.

The International Association for the Study of Pain (IASP) at <http://www.iasp-pain.org> was founded in 1973, and is the largest, multidisciplinary, international association in the field of pain. The IASP is dedicated to researching pain and improving the care of patients with pain. The Web site provides a variety of information, including upcoming conferences and continuing education programmes, links to pain journals, and patient information.

The Neuropathy Association in the USA has developed a new Web site at <http://www.neuropathymd.org> to help physicians diagnose neuropathy. Its key feature is an interactive guide on neuropathic pain syndromes. The guide is designed to assist physicians in evaluating and diagnosing patients with neuropathy.

CONFERENCE CALENDAR

MEETING	17 th Annual Congress of the Hong Kong Society for Surgery of the Hand	Australian Society for Geriatric Medicine Annual Scientific Meeting	Hong Kong College of Anaesthesiologists & Asian Oceanic Society of Intravenous Anaesthesia Combined Scientific Meeting in Anaesthesiology
LOCATION	Hong Kong	Melbourne, Australia	Hong Kong
DATE	June 7-8, 2003	June 16-18, 2003	September 26-28, 2003
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