

Challenges in Neuropathic Pain

Welcome to the new-look *Challenges in Neuropathic Pain*, a newsletter from the Multidisciplinary Panel on Neuropathic Pain (MPNP). Included in this 11th issue is a summary of the recommendations from the MPNP on the management of neuropathic pain in spinal cord pathologies and part 2 of the series on drugs for neuropathic pain – in this issue, tricyclic antidepressants are discussed. Visit www.neuropainhk.org for back issues of *Challenges in Neuropathic Pain* and to download patient education materials and recommendations from the panel on various neuropathic pain syndromes.

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Forward any comments
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Recommendations on the Management of Neuropathic Pain due to Spinal Cord Pathologies

Pain is a common symptom of several spinal cord pathologies, including traumatic spinal cord injuries (SCIs), intramedullary tumours, syringomyelia and multiple sclerosis (Table 1). It also frequently arises following spinal cord trauma, for example, inflicted in a car accident.^{1,2} Other causes include iatrogenic pain (such as from surgery), inflammation, tumours, vascular disease and congenital conditions.²

Around 60% to 70% of SCI patients will develop pain and about one third will report severe pain.² These patients may also experience dysaesthesia and allodynia. Collectively, the prevalence of spinal cord pain or dysaesthesia may reach 77% and allodynia may be present in almost half of patients.³

Spinal cord pain is generally chronic and debilitating, with a large proportion of sufferers (60% to 65%) experiencing continued severe pain for more than 6 months.^{2,4} Spinal cord pain is associated with poor quality of life, stress, depression and other psychological problems.⁵

Table 1. Spinal cord pathologies that may cause neuropathic pain

Compressive lesions

- Spinal cord injury
- SCI
- Haematomyelia
- Syringomyelia
- Primary and metastatic intramedullary tumours

Noncompressive lesions

- Spinal cord infarction
- Arteriovenous malformation
- Infectious myelitis, including neurosyphilis
- Acute transverse myelitis and multiple sclerosis
- Vitamin B₁₂ deficiency
- Idiopathic progressive necrotic myelopathy
- Familial spastic paraplegia
- Iatrogenic causes

Table 2. Distinctions between radicular and central pain in neuropathic spinal cord pain

Radicular pain or at-level pain

- Occurs at the level of the spinal cord lesion or two segments above or below⁵
 - Dermatomal distribution⁵
- Pain may be due to:
- Nerve root involvement
 - Changes within the spinal cord
 - Changes within supraspinal structures

Central pain or below-level pain; also, deafferentation pain

- Generally diffuse; present at least three dermatomal segments below the lesion level⁵
- Due to lesions in the spinothalamic pathways⁸
- Characterized by abnormal pain perception (generally described as burning and ice-like) and loss of spinothalamic pathway-mediated sensations^{8,9}
- May be mediated by up-regulation of neuronal activity⁹
- Occurs in 10% to 20% of SCI patients⁹

Pain associated with spinal cord lesions may be classed into four types: musculoskeletal, visceral, neuropathic and other.^{5,6} These recommendations focus on the management of neuropathic spinal cord pain.

Classification of neuropathic spinal cord pain

Spinal cord pain of neuropathic aetiology may be further subdivided, mainly into radicular pain and central pain.⁷ The distinctions between radicular and central pain are shown in Table 2.

Neuropathic pain associated with allodynia is more common in patients with incomplete spinal cord lesions, central cord syndrome or cervical cord involvement.⁴ Patients who develop neuropathic pain soon after spinal injury are more likely to develop ongoing pain, which is more likely to be severe.¹⁰

Management of neuropathic spinal cord pain

Assessment and diagnosis

The Transverse Myelitis Consortium Working Group has proposed a diagnostic algorithm for acute transverse myelitis, which can help to identify patients with neuropathic pain due to spinal cord lesions (Figure).¹¹ Key points for assessment and diagnosis are summarized below.

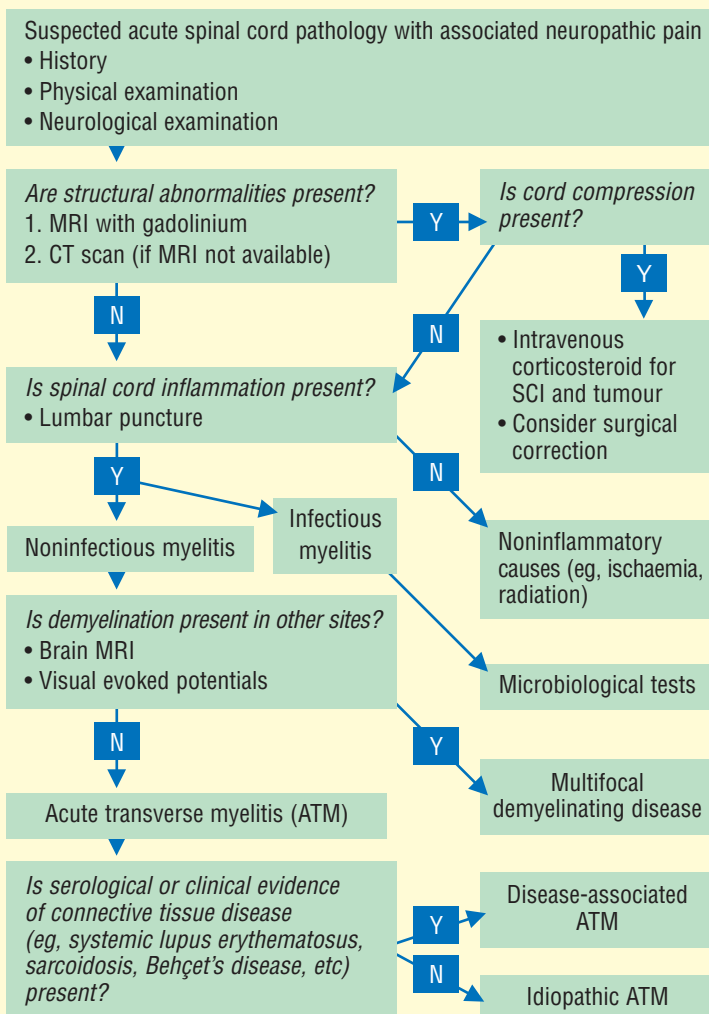
- Determine nature of the spinal cord lesion: a thorough clinical history, physical examination and neurological examination should be conducted for all patients with SCI and neuropathic pain symptoms.
- Identify and manage emergent conditions promptly (eg, spinal cord compression).¹¹ Assessment should then be directed at:
 - Localizing the lesion (ie, neurological level); and
 - Qualifying and quantifying pain, including differentiation between at-level and below-level pain.^{7,12} Sensory testing should be considered.¹²
- Determine presence of a structural cause: diagnostic imaging procedures (eg, magnetic resonance imaging [MRI], preferably with gadolinium contrast, or computed tomography [CT]-myelography) should be part of the initial evaluation.¹¹
- Distinguish between an inflammatory and noninflammatory cause: in the absence of any contraindication, a lumbar puncture (with analysis of cerebrospinal fluid [CSF] cell count, differential count, protein, glucose, intrathecal antibodies and cytology) may be performed.¹¹
 - The presence of inflammatory conditions may warrant further examinations to identify demyelination in the spinal cord or elsewhere. Other ancillary diagnostic procedures may be performed whenever indicated.

Treatment

Following diagnosis of neuropathic pain due to SCI, a multidisciplinary approach should be taken to rehabilitation.¹³ Many patients achieve significant pain relief from physical therapy.¹⁴ Primary treatment of neuropathic pain due to spinal cord lesions should target the underlying cause (eg, surgery for certain structural abnormalities) and other neurological sequelae (eg, motor deficits, incontinence).

- SCI causing compression should be treated within 8 hours of compression, if possible.¹³ Methyl-prednisolone may be given as a 30 mg/kg-bolus dose then maintained at a dose of 5.4 mg/kg/hour. If initiated within 3 hours, treatment should be maintained for 24 hours; maintain treatment for 48 hours if initiated between 3 and 8 hours after injury. If neuropathic pain is due to direct compression by tumour, antineoplastic

Figure. Diagnostic algorithm for patients with neuropathic pain due to spinal cord lesions¹¹



Adapted from the Transverse Myelitis Consortium Working Group recommendations

treatment may reduce the size of the tumour and provide pain relief.¹⁵

- There is scant evidence for the benefits of nonsteroidal anti-inflammatory drugs in neuropathic pain arising from spinal cord lesions, and these drugs do not merit further mention in these recommendations.¹⁶
- Anticonvulsants and opioids are perceived by SCI patients as the most effective analgesics, and either may be used as first-line treatment for neuropathic pain due to spinal cord lesions.^{14,17-21} Patients receiving opioids or other analgesics may also be given an add-on anticonvulsant (eg, gabapentin, pregabalin) to improve pain control.^{22,23}
- Intravenous ketamine may be used as third-line therapy, but patients receiving ketamine should be monitored meticulously for side effects.^{20,24,25}
- Patients who respond poorly to oral, transdermal or intravenous analgesics may be considered for invasive procedures, such as

intrathecal drug administration, neurostimulation (eg, spinal-cord stimulation [SCS], electroacupuncture) and dorsal root entry zone lesioning (DREZotomy).^{8,26-28} SCS should be tried before DREZotomy, as it is a less invasive procedure.

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CASE PRESENTATION

In this issue, a case of neuropathic pain associated with Devic's disease is discussed. Reviewing case studies will help to improve your diagnostic approach and increase your understanding of how to select treatment strategies for neuropathic pain.

Devic's Disease

Presenting symptoms

A 25-year-old woman presented within 24 hours of sudden-onset blindness in the right eye. She was a nonsmoker with no significant medical history.

Objective findings

Clinical examination revealed a blurred optic disc, a Marcus Gunn pupil and delayed visual evoked potential of the right eye. MRI of the brain showed a swollen right optic nerve, but no other abnormalities. Treatment with cortico-steroids reversed the loss of vision; however, visual acuity in the right eye remained poor.

Fifteen months later, she returned complaining of abdominal pain and distention, and she subsequently developed paraparesis of her lower limbs. Physical examination revealed sensory loss at approximately T6 and below, and flaccid lower limbs. MRI revealed myelitis from T6 to T10. Devic's disease was diagnosed.

Management

After a further course of corticosteroids and rehabilitation, she was able to walk with a frame. Two months later, the patient complained of occasional spasm and burning dull pain in her lower limbs. The pain gradually worsened, interrupting her normal sleep pattern. Amitriptyline and carbamazepine were commenced, but did not relieve her symptoms and were subsequently discontinued. She was then prescribed baclofen for skeletal-muscle spasticity and pregabalin for neuropathic pain, which resulted in symptom improvement. Maintenance therapy controls her condition.

Discussion

Devic's disease is a rare, chronic and debilitating central nervous system disease. Patients may experience repeated episodes of inflammation and damage to the myelin that almost exclusively affect the optic nerve and spinal cord. Patients can experience varying paraparesis and paralysis. Short-duration skeletal-muscle spasms of 15 seconds to 2 minutes may occur several times a day, and the neuropathic pain associated with this condition may be constant and disabling. In most cases of Devic's disease, spasms will respond to therapy with muscle relaxants, and neuropathic pain will respond to anticonvulsant medication, such as pregabalin.

Q & A

Forward your questions on diagnosis, treatment or management of neuropathic pain to the Multidisciplinary Panel on Neuropathic Pain at mpnp@asia.cmpmedica.com or fax to +852 2559 6910.

Are there any international guidelines on the management of neuropathic pain?

In 2004, the American Academy of Neurology published evidence-based treatment recommendations for postherpetic neuralgia (PHN) [Dubinsky RM, et al. *Neurology* 2004;68:959-965].

Also in 2004, the Wisconsin Medical Society Task Force on Pain Management published guidelines on chronic pain management in the *Wisconsin Medical Journal*. A PDF copy of these guidelines can be downloaded from: <http://www.wisconsinmedicalsociety.org/uploads/wmj/ACFC7.pdf>.

The American Geriatric Society Panel on Persistent Pain in Older Persons published clinical practice guidelines in the *Journal of the American Geriatric Society* in 2002. A PDF copy of this publication can be downloaded from: <http://www.americangeriatrics.org/products/positionpapers/JGS5071.pdf>.

Locally, the Multidisciplinary Panel on Neuropathic Pain (MPNP) continues to regularly review the literature and recommend guidelines for managing various neuropathic pain conditions in Hong Kong. These have been published in *Medical Progress* and summarized in issues of this newsletter. To receive more information, contact MPNP at: mpnp@asia.cmpmedica.com.

DRUGS FOR THE TREATMENT OF NEUROPATHIC PAIN

As in issue 10 of the newsletter, we again review a different class of drugs useful in the management of neuropathic pain. Part 2 of this series examines the evidence for tricyclic antidepressants.

Part 2 – Tricyclic antidepressants

In the pharmacological treatment of neuropathic pain, tricyclic antidepressants (TCAs) are frequently prescribed and often recommended as first-line therapy.^{1,3} TCAs include amitriptyline, imipramine, clomipramine, nortriptyline and desipramine.

TCAs exert their analgesic effect – which is independent of their antidepressive effect² – by inhibiting the reuptake of norepinephrine and serotonin.³ Well-designed, randomized, controlled clinical trials have shown that TCAs have efficacy in the following neuropathic pain syndromes: PHN, diabetic peripheral neuropathy, central poststroke pain and complex regional pain syndrome II.^{3,4} However, there is little, or inconclusive, evidence for their benefit in syndromes such as trigeminal neuralgia or neuropathic pain arising from SCI.^{3,4}

Of the TCAs, amitriptyline has been the most studied for neuropathic pain.² However, nortriptyline and desipramine have similar efficacy in some neuropathic pain syndromes, such as PHN,^{5,7} and are generally better tolerated.²

The primary problem with the use of TCAs is their adverse-event profile and numerous contraindications: TCAs must be used cautiously in patients with a history of cardiovascular disease, glaucoma, urinary retention or autonomic neuropathy.² In elderly

patients, TCAs may cause balance problems and cognitive impairment, and amitriptyline is not recommended in elderly patients because of the significant risk of adverse events.² TCAs must also be used cautiously when there is a risk of suicide or accidental death from overdose, and physicians should be mindful of the effects arising from the inhibition of cytochrome P450 2D6 by TCAs.² In general, the most common adverse events with TCA therapy are sedation, anticholinergic effects (ie, dry mouth, constipation) and hypotension. To decrease adverse events and increase patient adherence to treatment, TCAs should be initiated at low dosages – 10 to 25 mg in a single dose at bedtime – and then titrated every 3 to 7 days by 10 to 25 mg/day, as tolerated.²

Part 1 of this series can be found on www.neuropainhk.org/newsletter.asp – Issue 10.

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LITERATURE REVIEW

Coen PG, Scott F, Leedham-Green M, et al. *Predicting and preventing post-herpetic neuralgia: Are current risk factors useful in clinical practice?* *Eur J Pain* 2006. Jan 19; [Epub ahead of print]

Previously, clinical trials have identified five clinical factors – 1) older age; 2) female gender; 3) the presence of prodromal pain; 4) the extent of rash; and 5) pain severity at onset – to be independent risk factors for PHN, a debilitating neuropathic pain condition that may occur following herpes zoster. However, how useful are these risk factors to the general physician in everyday clinical practice for predicting PHN? This recently published, observational study, which followed 280 herpes zoster cases presenting to general practitioners (GPs) in England, sought to address precisely this question.

The results may come as a surprise to some: of the five clinical factors listed above, only older age (>50 years) and severity of pain (visual analogue score >5) correctly identified all subjects with PHN at

3 and 6 months, respectively. However, the specificity of this prediction was low because as many as 81% and 85% of those older than 50 years recovered within 3 and 6 months, respectively. Ophthalmic involvement was also predictive of PHN at 6 months.

The authors concluded that other than age and level of pain, risk factors derived from clinical trial data are not useful in helping GPs to target antiviral and early antidepressant or antiepileptic therapy to those at most risk of PHN. Early identification of those patients older than 50 years with greatest risk of PHN would improve the use of these drugs but, as this study shows, it would be prudent for GPs to assess factors other than clinical features alone for predicting and preventing PHN.

CONFERENCE CALENDAR

Annual Meeting of the Korean Pain Research Society

10 September 2006, Seoul, Korea

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