

NEUROPATHIC PAIN



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Forward any comments on this newsletter to the Multidisciplinary Panel on Neuropathic Pain at mpnp@asia.cmpmedica.com

Challenges in Neuropathic Pain is a newsletter brought to you by the Multidisciplinary Panel on Neuropathic Pain (MPNP). This issue features a summary of the recommendations from the MPNP on neuropathic pain associated with complex regional pain syndrome, and a case presentation on facial pain. The regular features include a review of the efficacy of gabapentin in painful HIV-associated sensory neuropathies, a discussion about fibromyalgia, useful Web sites and a calendar of upcoming conferences, to help keep Hong Kong clinicians abreast of the latest news in neuropathic pain.

Recommendations on the Management of Complex Regional Pain Syndrome

Complex regional pain syndrome (CRPS), also known previously as reflex sympathetic dystrophy, causalgia, algodystrophy, Sudeck's atrophy and shoulder-hand syndrome, is an uncommon and poorly understood neuropathy that normally affects the limbs. It is characterized by pain and altered sensation; motor dysfunction (weakness, tremor, dystonia, decreased range of motion); trophic changes of the skin, nail, hair and muscle; and vasomotor and autonomic alterations (oedema, and changes in skin temperature, colour and sweating pattern).¹ Signs and symptoms may progress if the condition is left untreated; some patients experience debilitating pain, muscle atrophy, and permanent joint and skin damage with advanced disease. Psychological disturbances, such as anxiety, depression and fear-avoidance, often accompany CRPS.

Women are more likely to develop CRPS than men. CRPS can affect all age groups, but is most common in those aged 40 to 60 years. Reports indicate that CRPS occurs in 1% to 2% of post-fracture patients and, after peripheral nerve injury, in 2% to 5% of patients.² No cause can be identified in 10% to 26% of cases.^{2,3}

The International Association for the Study of Pain (IASP) classifies CRPS as⁴:

- CRPS type I – occurs after minor injury that may be unnoticed by the patient; associated nerve injury may not be obvious.
- CRPS type II – associated with an identifiable nerve injury, often following trauma or surgery.

Diagnosing CRPS

The diagnosis of CRPS is often complicated by variability in presenting symptoms and difficulty identifying causative lesions. CRPS types I and II may or may not be associated with sympathetic-maintained pain (SMP). The IASP published the following consensus-based diagnostic criteria for CRPS⁴:

1. The presence of an initiating noxious event or a cause for immobilization. For CRPS type II, a known nerve injury should be present.
2. Continuing pain, allodynia or hyperalgesia disproportionate to the injury's severity.
3. Evidence at some time of oedema, changes in skin blood flow or abnormal sudomotor activity in the region of pain.
4. CRPS is excluded by the presence of conditions that would otherwise account for the degree of pain or dysfunction.

However, a validation study of these criteria indicated significant overdiagnosis and proposed a more specific set of criteria (Table) to discriminate between CRPS and other types of neuropathic pain.⁵

Patient evaluation for CRPS should include:

- A review of medical history (including pain patterns, onset of symptoms and associated injury).
- Physical examination (for trophic and sudomotor changes).
- Neurological examination and electrodiagnostic testing, if appropriate.
- Bone scintigraphy or x-ray to identify any bone changes.
- Thermography (for blood flow and skin temperature changes).
- Sudomotor evaluation measuring sweat output may be helpful.

Treating CRPS

General recommendations

Patient outcomes are improved if treatment is started at an early stage: patients should be referred as soon as possible to pain specialists or physicians with experience in managing CRPS. In cases associated with trauma, surgical restoration (eg, decompression of a compromised neural structure) is beneficial and, if appropriate, should be performed immediately.

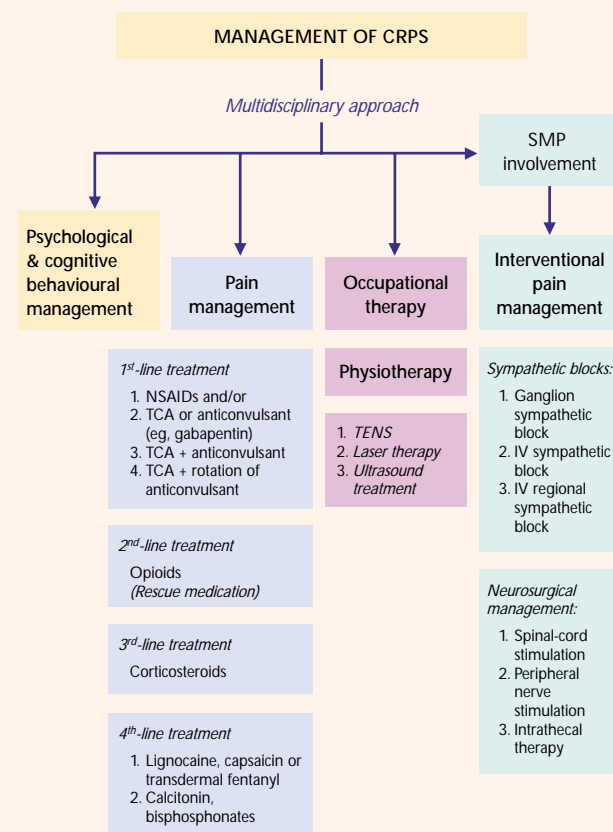
Most children with recent-onset CRPS will improve spontaneously and require conservative management only. In adults, a holistic programme combining both pharmacological and nonpharmacological techniques may achieve remission. An early programme of physical and occupational therapy, especially for at-risk patients, will improve pain control and mobility. Psychological support and cognitive behavioural management programmes can help patients manage their pain, and reduce depression and dependence on healthcare services. The Rehabilitation Pathway, adapted from that proposed by the International Coalition on Neuropathic Pain (ICNeP),⁶ provides a stepwise approach combining different modalities to optimize CRPS management (Figure).

Pharmacological therapy

Although published evidence for drug efficacy in CRPS is lacking, drugs used in CRPS therapy have been found effective in a variety of neuropathic pain syndromes. In cases associated with injury and marked inflammation, nonsteroidal anti-inflammatory drugs, particularly those with significant activity against bradykinin and prostacyclin (eg, ketoprofen), are useful in the acute phase.^{7,8}

Gabapentin is effective in treating other neuropathic pain syndromes, such as painful diabetic neuropathy^{9,10} and postherpetic neuralgia,^{11,12} and several studies have indicated it may also be useful in CRPS. A recent placebo-controlled crossover trial with two 3-week treatment periods separated by a 2-week washout period revealed gabapentin (up-titrated to 600 mg tid) provided significant pain relief

Figure. The Rehabilitation Pathway⁶



NSAIDs, nonsteroidal anti-inflammatory drugs; SMP, sympathetic-maintained pain; TCA, tricyclic antidepressant; TENS, transcutaneous electrical nerve stimulation; IV, intravenous.

(measured by visual analogue scale [VAS]) in CRPS type I patients in the first treatment period.¹³ Gabapentin therapy also significantly reduced CRPS-associated sensory deficits in the affected limb more effectively than placebo (Von Frey monofilament skin application scores: 25.0 vs 16.8, $p < 0.05$). Older anticonvulsants, such as phenytoin and carbamazepine, have a less favourable adverse-effect profile than gabapentin.^{14,15}

Tricyclic antidepressants (TCAs), especially amitriptyline, have also been used effectively in treating various neuropathic pain syndromes.¹⁶ Clomipramine improved pain in patients with dysaesthesia, hyperpathia and CRPS.¹⁷ However, side effects can limit the use of TCAs in some patients.

Both TCAs and anticonvulsants require slow dosage titration (up to 8 weeks to reach maximal dose) to minimize side effects. When the response to TCAs or anticonvulsants is unsatisfactory, combining a TCA with an anticonvulsant may be effective. If the

Table. Proposed CRPS diagnostic criteria⁵

1. Continuing pain that is disproportionate to any inciting event
2. The patient must report at least one symptom in each of the four categories below
3. The patient must display at least one sign from two or more of the four categories below

Sensory	Vasomotor	Sudomotor/oedema	Motor/trophic
<ul style="list-style-type: none"> • Hyperalgesia • Allodynia 	<ul style="list-style-type: none"> • Temperature asymmetry • Skin colour changes and/or asymmetry 	<ul style="list-style-type: none"> • Oedema • Sweating changes and/or asymmetry 	<ul style="list-style-type: none"> • Decreased range of motion • Motor dysfunction (weakness, tremor, dystonia) • Trophic changes (hair, nail, skin)

initial medications do not provide sufficient analgesia, short-term rescue therapy with an opioid is an option.¹⁸ A trial of corticosteroids, lignocaine, capsaicin, transdermal fentanyl, calcitonin or bisphosphonates should also be considered for patients who do not respond to first- or second-line therapies.

Interventional pain management

When pain from CRPS is refractory to pharmacotherapy and conservative pain management procedures, spinal-cord stimulation, implantable intrathecal drug-delivery systems or peripheral nerve stimulation may be considered.^{19,20} Long-term intraspinal morphine administration has been effective in patients with intractable CRPS.²⁰ However, when considering these procedures, a thorough medical and psychological assessment should be performed to ensure optimal patient selection for favourable outcomes.

Evidence supporting the use of sympathetic blocks in CRPS is poor. Response from sympathetic blockade is often brief, limiting its use to diagnostic purposes or to facilitate physical rehabilitation in patients with SMP.²¹ Neurolytic or surgical sympathectomy may provide short-term improvement but because of the destructive nature of these procedures, risks often outweigh benefits. Hence, these procedures are generally reserved for terminally ill patients.

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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 facial pain is discussed.



Facial pain from tooth implants

Presenting symptoms

A 75-year-old woman presented with a 2-year history of intermittent sharp pain on the left side of her face. Light touch and chewing aggravated the pain, as did washing her face with cold water. She did not experience pain at rest.

Objective findings

The physical examination was unremarkable, and a brain CT scan to rule out lesions pressing on the trigeminal nerve was normal.

Management

The patient was prescribed simple analgesia (paracetamol), then a tricyclic antidepressant (amitriptyline 50 mg tid), followed by anticonvulsants (carbamazepine 200 mg bid and subsequently gabapentin 600 mg tid). These medications did not provide effective pain relief, and stronger analgesics such as tramadol and Dologesic gave partial pain relief.

Further questioning and a review of the patient's history revealed a left upper molar extraction and a tooth implantation procedure 2 years previously, just before the onset of pain. The patient was referred to a dental surgeon, who removed the implanted left molar. The patient has since been pain-free.

Discussion

On diagnosing facial pain that resembles a trigeminal nerve disorder – particularly when symptoms appear unresponsive to pain medications – care should be taken to rule out dental pathologies. In this case, the dental implant, which directly fastens to a patient's jaw, had probably damaged the surrounding tissue and caused the intermittent pain. Physicians should take an accurate medical history to highlight any events or conditions that could be the inciting cause of the pain; this will help to appropriately target pain management strategies.

Source: MPNP members

PAIN WEB SITES

Stop Pain (www.stoppain.org) is the Web site of the Department of Pain Medicine and Palliative Care of the Beth Israel Medical Center in New York. It offers resources for health professionals involved in the clinical management of chronic pain. Physicians can find e-learning opportunities, browse a multimedia library on pain disorders, examine tools helpful in providing palliative care or download slide presentations on pain topics. For resources on integrative pain medicine – the combination of traditional pain management with complementary methods – visit www.healingchronicpain.org. This site offers recommendations on novel therapeutic approaches that can help physicians provide a holistic approach to pain management.

LITERATURE REVIEW

Hahn K, Arendt G, Braun JS, et al. A placebo-controlled trial of gabapentin for painful HIV-associated sensory neuropathies. *J Neurol* 2004;251:1260-1266.

The effectiveness of the anticonvulsant gabapentin in painful HIV-associated sensory neuropathies (HIV-SNs) has been documented in anecdotal reports. Although the mechanism of action remains unclear, it is possible gabapentin may affect α 2- δ calcium channels and inhibit ectopic discharge activity from injured nerves.

A multicentre, randomized, double-blind, placebo-controlled study evaluated the efficacy of gabapentin in the treatment of painful HIV-SNs in 26 patients. After a 1-week screening phase, patients were randomized to receive either gabapentin or placebo in a double-blind design. Gabapentin dosage and matching placebo were titrated (400 mg/day every 4 days) over 2 weeks up to 1,200 mg/day in three divided doses, then up to 2,400 mg/day over the next 2 weeks, if necessary. After a 4-week period, the study medication was unblinded, and patients were given the choice to begin, maintain or increase the gabapentin dosage up to 3,600 mg/day in a 2-week open-treatment phase. The primary outcome measure was the efficacy of gabapentin in improving pain symptoms in HIV-SNs. A secondary efficacy measure was the median sleep interference score. Both parameters were measured in a patient-reported diary using a 10-cm VAS.

Gabapentin-treated patients reported significant pain relief after 4 weeks ($n=15$, median baseline week=5.1, median fourth week of treatment=2.85, -44.1% [Wilcoxon-test; $p<0.05$]) and a significant decrease in the sleep interference score (median baseline week=4.5, median fourth week of treatment=2.3, -48.9% [Wilcoxon test, $p<0.05$]). There were no significant improvements in the placebo group. Gabapentin was generally well tolerated, with somnolence the most frequently reported side effect. Hence, gabapentin was more effective than placebo in reducing pain and sleep interference in patients with HIV-SNs.

CONFERENCE CALENDAR

11th World Congress on Pain

21-26 August 2005, Sydney, Australia

Congress Secretariat:
Tour Hosts Pty Limited, GPO Box 128,
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Web site:
www.iasp-pain.org/05cong.html

Combined Scientific Meeting in Anaesthesiology 2005

27-28 August 2005, Hong Kong

A satellite meeting of the 11th World Congress on Pain

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E-mail: csm2005@icc.com.hk
Web sites:
www.hkca.edu.hk/csm2005.htm;
www.iasp-pain.org/05satellitesymp.html

Q & A

E-mail your questions on neuropathic pain to the Multidisciplinary Panel on Neuropathic Pain at mpnp@asia.cmpmedica.com.

What is fibromyalgia?

Fibromyalgia syndrome (FMS) is a condition commonly characterized by generalized pain, fatigue, disturbed sleep and unexplained somatic symptoms, such as occipital headaches, morning stiffness, digital paraesthesia and chest wall pain. However, the hallmark of this syndrome is diffuse pain radiating from the axial skeleton to muscles and muscle-tendon junctions of the neck, shoulders, hips and extremities. Pain thresholds are reduced, and many patients exhibit generalized allodynia. Depression, anxiety and other psychiatric comorbidities are commonly present, and cognitive-behavioural, environmental and sociocultural variables play important roles. FMS is not a fictitious or psychosomatic disorder, and the associated pain and fatigue have demonstrable pathophysiological bases. The diagnostic criteria for FMS include:

1. Widespread pain for at least 3 months; and
2. Pain elicited by digital palpation with a pressure equivalent to 4 kg at 11 or more of 18 anatomically defined tender points.

The cause of FMS remains unknown. However, recent evidence has associated FMS with low serotonin levels and elevation of substance P. Dysfunction of immunoregulatory mechanisms, central processing of nociceptive signals, and the hypothalamic-pituitary-adrenal axis have also been implicated.

The goal of therapy is palliation of symptoms. Pain, fatigue, sleep disturbance, depression and anxiety respond to a multifaceted therapeutic approach combining pharmacological and nonpharmacological interventions, such as graded aerobic exercise and stress management techniques. Diffuse pain may be treated with low-dose TCAs, often in combination with a centrally-acting muscle relaxant. Marked allodynia and hyperalgesia often respond to anticonvulsants, such as gabapentin.

Thank you

The Multidisciplinary Panel on Neuropathic Pain would like to thank those readers who responded to the survey distributed with issue 8 of *Challenges in Neuropathic Pain*. Your feedback and suggestions were most welcome, and have provided useful ideas for topics to cover in future issues. Forward any further comments on the newsletter to the panel at mpnp@asia.cmpmedica.com.

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