The feature article in this issue of Challenges in Neuropathic Pain reviews the problem of persistent post-surgical pain and the prevalence of and risk factors for post-surgical complex regional pain syndrome. In his regular column, Professor Rainer Freynhagen outlines the latest on neuropathic cancer pain, and the case presentation is on a patient with persistent somatoform pain disorder. Visit www.neuropainhk.org for more resources from the MPNP on neuropathic pain.

Persisting post-surgical pain with a focus on complex regional pain syndrome

Surgical interventions cause tissue injury and inflammation, resulting in acute post-operative pain. Persistent or chronic pain can occur if subsequent modulation of the peripheral and central nervous systems occurs. Incidence rates of persistent post-surgical pain range from 5% to 85%, depending on the type of surgery. Risk factors include pre- and immediate post-operative pain, intraoperative nerve damage, age, type of anaesthesia, and genetic and psychosocial factors. Chronic post-surgical pain can be neuropathic, visceral, somatic or mixed in origin. Thoracic, arthroscopic and abdominal surgeries carry a high risk for persistent post-surgical pain. A subset of persistent post-surgical pain is defined as complex regional pain syndrome (CRPS), which usually affects a single limb after surgery or trauma to the ankle, hand, wrist or radius. CRPS can persist for several years, and the lasting pain and disability can severely impact patients’ quality of life and ability to work.

Definition and diagnosis of CRPS
CRPS is divided into two subtypes. CRPS type I occurs without an obvious associated injury to the nerve and CRPS type II follows a distinct nerve injury. Both types of CRPS present with typical signs that are characteristic of neuropathic pain, such as spontaneous, burning pain, allodynia and pain occurring in the area with sensory abnormalities.

CRPS shows variable progression over time and is associated with abnormal peripheral sensory and autonomic nerve function, immune activation, and changes in central signal processing. Historically, the diagnosis of CRPS was hampered by the absence of standardized diagnostic criteria. To address these limitations, an international
Table. Clinical diagnostic criteria for CRPS\textsuperscript{11}

1. Continuing pain disproportionate to any inciting event (often described as tearing, burning or stinging, which may be diffuse and located deep within the extremity)
2. Three out of four of the following symptom categories:
   i. Sensory (hyperalgiesia and/or allodynia)
   ii. Vasomotor (skin colour changes/asymmetry and/or temperature asymmetry)
   iii. Sudomotor/oedema (oedema and/or sweating changes/asymmetry)
   iv. Motor/trophic (reduced range of motion and/or motor weakness and/or trophic changes in nails, skin or hair)
3. At least one sign at the time of evaluation in two or more of the following categories:
   i. Sensory
   ii. Vasomotor
   iii. Sudomotor/oedema
   iv. Motor/trophic
4. No other diagnosis better explains the signs and symptoms

consensus meeting was held in Budapest in 2003, at which modified criteria were proposed. These Budapest Criteria\textsuperscript{11} (Table) are used to diagnose CRPS with excellent sensitivity (99%) and a specificity of 68%.\textsuperscript{12}

**Epidemiology and risk factors for CRPS post-surgery**

The incidence of CRPS varies according to the diagnostic criteria used, and has been reported at 17–26 per 100,000 person-years in Europe.\textsuperscript{13} A retrospective cohort study based on primary care data in the Netherlands showed that most CRPS cases involved trauma (44% fracture, 18% ligamentous injury and 12% surgery), and that CRPS occurred most commonly in women (gender ratio 3–4 : 1), between the ages of 50 and 70 years.\textsuperscript{13}

A number of studies have addressed the prevalence of and risk factors for CRPS following surgery. A prospective questionnaire-based cohort study of all patients undergoing primary surgery for ankle or wrist fractures at two Danish hospitals showed that 18.9% of patients experienced persistent post-surgical pain 1 year after surgery, and 4.0% fulfilled the diagnostic patient-reported research criteria for CRPS.\textsuperscript{2} All the CRPS patients were women, and 60% of them had suffered ankle fractures.\textsuperscript{2} This incidence of CRPS was similar to the 3.8% observed in an Australian study of a prospective cohort of 1,549 consecutive patients who were non-surgically treated for wrist fracture.\textsuperscript{14} Greater pain experienced from the fracture (pain score of ≥5 on a 0–10 numerical rating scale) was predictive of developing CRPS 4 months later.\textsuperscript{15} A Korean study of 498 patients who had surgery following a distal radius fracture showed that 8.8% developed CRPS I within 6 months of surgery,\textsuperscript{9} although rates of up to 37% have also been reported.\textsuperscript{12} Women and those with a high-energy fracture type or significant trauma were significantly more likely to develop CRPS.\textsuperscript{9} In a Japanese study, 39 patients were diagnosed with CRPS out of a cohort of 185,378 who underwent surgery for limb fractures;\textsuperscript{16} fractures of the distal forearm and longer duration of anaesthesia were associated with higher incidence rates of CRPS.

Other studies have shown that hand surgery is also a common cause of CRPS, with rates of 5% to 40% reported after fasciectomy for Dupuytren contracture, and 28% after carpal tunnel surgery.\textsuperscript{5}

**Mechanisms underlying pain in CRPS**

CRPS is a multifactorial syndrome involving the sensory, motor, and autonomic nervous systems, cognitive deficits, changes in mood, anxiety, bone demineralization, skin growth changes, and vascular dysfunction.\textsuperscript{3} The onset of CRPS is preceded by trauma or surgery that results in an inflammatory response and neurogenic inflammation, which can induce focal osteopenia in the case of a fracture (Figure).\textsuperscript{16} Cytokine release from the inflamed region leads to peripheral sensitization, and ultimately central sensitization and maladaptive neuroplasticity, resulting in central motor symptoms. Central sensitization is thought to contribute to the chronicity of pain in CRPS.\textsuperscript{16} Sympathetic pain is maintained by sympatho-afferent coupling.\textsuperscript{16} Finally, psychogenic stress can lead to increased release of catecholamines, which can generate and further exacerbate pain.\textsuperscript{16}

**Figure. Multiple mechanisms underlying CRPS necessitate a multidisciplinary approach to management.**\textsuperscript{16}

- **Physiotherapy**
  - Occupational therapy
  - Graded motor imagery
- **Intrathecal baclofen**
- **Analgetics** (gabapentin, tricyclic antidepressants, pregabalin, opioids, topical analgesia)
- **Combination of analgetics**
- **Disturbed body scheme**
- **Central motor symptoms, such as severe dystonia**
- **Spontaneous pain**
  - Hyperalgiesia
  - Allodynia
- **Central sensitization**
  - Sympatho-afferent coupling
  - Neurogenic inflammation
  - Inflammatory response
  - Peri¬
  - Neurogenic sensitization
  - Spontaneous pain
- **Maladaptive neuroplasticity**
- **Psychological symptoms**
  - Behavioural or cognitive–behavioural therapy
  - Sympathetically maintained pain
  - Focal osteopenia
- **Inflammatory signs**
  - Oedema
  - Redness
  - Heat
  - Pain
  - Dysfunction
- **Bisphosphonates**
  - Short-term treatment with corticosteroids
- **Sympathetic blocks**
- **Catecholamines**

Peripheral and central mechanisms (orange boxes) lead to typical signs and symptoms (blue), which can guide mechanism-based treatment options (green).

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3. At least one sign at the time of evaluation in two or more of the following categories:
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Management

The successful management of CRPS requires a multidisciplinary approach that involves pharmacotherapy, interventional therapy (such as sympathetic blocks or intrathecal baclofen administration), physiotherapy (including graded motor imagery), occupational therapy and psychological treatment (Figure). 16

It has been difficult to develop guidelines for the treatment of CRPS because of the limited number of trials available. 17 Difficulties in studying specific interventions include the need for multidisciplinary treatments, limited numbers of patients, differing diagnostic criteria, and the varying nature and duration of the clinical manifestations. Pharmacotherapies used for the treatment of CRPS include anti-inflammatory drugs and immunomodulators, anticonvulsants (eg, pregabalin, gabapentin) and neuremodulators, antidepressants and anxiolytics, opioids, N-methyl d-aspartate (NMDA) antagonists, antihypertensive agents and α-adrenergic antagonists, bisphosphonates and calcitonin. 17 An analysis of six Cochrane reviews and 13 non-Cochrane systematic reviews revealed low quality evidence that bisphosphonates, calcitonin or a daily course of intravenous ketamine may be effective for pain, and that graded motor imagery may be effective for pain and function. 17 Case series in adults and children suggest that gabapentin and pregabalin show efficacy against CRPS as part of a multidisciplinary approach, as does its ubiquitous empirical use for many neuropathic pain syndromes including CRPS. 17,18

While peri-operative use of pregabalin and gabapentin was shown to reduce the risk of chronic post-surgical pain in one meta-analysis, 19 another showed a reduction in the incidence of chronic post-surgical pain following treatment with ketamine, but not gabapentin or pregabalin, 20 and no specific evidence was presented to demonstrate prevention of CRPS.

Conclusions

Wrist and ankle fractures are among the most common surgically treated fractures in adults, and fracture-related surgery is associated with a risk of developing CRPS. 2 CRPS differs from many other neuropathic pain syndromes by having additional tissues and systems involved. 11 Pharmacotherapy is an important aspect of the multidisciplinary, mechanism-based approach required to manage CRPS, but formulating an evidence-based approach remains elusive due to lack of data resulting from difficulties in designing high-quality trials that involve multiple interventions.

References


CASE PRESENTATION

Persistent somatoform pain disorder

Clinical presentation

A 45-year-old man was referred to the psychiatric clinic because of low back pain that had persisted for 8 months after injury on duty (IOD). The patient was a construction site worker when he slipped and fell, landing on his buttock. He described the low back pain to be spontaneous, burning, and electric shock-like, with a tingling sensation. He also reported numbness in the painful area. There was only mild functional limitation, and his mobility was slightly limited. The patient’s recreational and interpersonal activities were slightly affected. The patient subsequently changed occupation, to a restaurant waiter. He reported insomnia and anxiety, and had a depressed mood as he was distressed by the pain. There was no other persistent mood feature, suicidal ideation or psychotic feature noted.

Investigations

The patient had undergone assessment by a neurologist and an orthopaedic surgeon. The neurological examination showed that there was reduced tactile sensation over the affected dermatome; the same area in which spontaneous pain occurred. Allodynia was demonstrated in the same area. MRI scan of the lumbar spine revealed no abnormality.

Diagnosis

The patient was diagnosed with persistent somatoform pain disorder, with comorbid insomnia, depressive and anxiety features. This diagnosis is based on the World Health Organization (WHO) International Classification of Diseases and Health Related Problems Tenth Revision (ICD-10) diagnostic criteria of psychiatric disorders. 1 Etiological factors include IOD-related physical symptoms and consequent functional disabilities.

Management

The patient was commenced on a tricyclic antidepressant (TCA) – amitriptyline 25 mg nocte – to treat his chronic pain and improve his mood and insomnia. However, he suffered from side effects, which were constipation and blurred vision. He was switched to pregabalin 25 mg om and 50 mg nocte, which improved his pain, insomnia, mood and function.

Discussion

According to the WHO ICD-10 diagnostic criteria for psychiatric disorders, persistent somatoform pain disorder refers to persistent severe and distressing pain for at least 6 months, which cannot be explained adequately by evidence of physiological cause or a physical disorder, and which is consistently the main focus of the patient’s concern. 1

The patient’s chronic pain could not be fully explained by a pathological cause. Psychological factors came into play to contribute to the etiology. His pain also had a neuropathic component, and the chronic pain affected his sleep and caused distress. Pregabalin and TCAs are recommended as first-line treatment for neuropathic pain by various international treatment guidelines. 2,4 However, TCAs are associated with many intolerable side effects. Pregabalin is also recommended to treat generalized anxiety disorder (GAD) by various international treatment guidelines. 5,6

References


Source: MPNP members
Neuropathic cancer pain: A different strategy needed?! 

The World Health Organization reported that in 2012 there were more than 14 million new cases of cancer, 8.2 million cancer deaths, and 32.6 million people living with cancer (within 5 years of diagnosis) worldwide.1 More than 60% of the world’s total new annual cases occur in Africa, Asia, and Central and South America. These regions account for 70% of the world’s cancer deaths.1 Pain is one of the most debilitating and disastrous experiences encountered by cancer patients at one point of their illness and mostly remains underreported and undertreated. Overall, around 75% of patients with metastatic or advanced-stage cancer develop severe pain which significantly compromises their quality of life.2 The Figure shows a scintigraphy of metastasis of a brain tumour.

Neuropathic cancer pain (NCP) is widely recognized as a common consequence of cancer and recent reviews report a prevalence ranging from 19-40%,3 including mixed cancer and recent reviews report a prevalence ranging from 19-40%,3 including mixed pain syndromes and is often multifactorial in aetiology.4,5 The majority of neuropathic pain in cancer patients arises as a direct result of tissue destruction by tumour or metastasis and invasion of nervous and bony structures.2 It’s known that metastatic cancer cells can invade the sensory c-fibres or activate osteoclasts responsible for bone lysis leading to de-afferentation and neuropathic pain components. Unfortunately cancer is frequently complicated by treatment factors such as surgery-induced scarring or nerve damage, chemotherapy- or radiotherapy-induced neuropathies, leading to NCP. Moreover paraneoplastic or infectious neuropathies are often a main concern during cancer treatment.4

No single sign or symptom is diagnostic of NCP; a combination of both is reliable. Classic neuropathic symptoms and descriptors have been included in screening tools for neuropathic pain developed in the last 15 years. The most widely used of these are the LANSS, the DN4 and painDETECT. Studies have shown that all screening tool items can significantly discriminate between neuropathic and nociceptive components in cancer patients, underpinning their validity.6,7 However, compared with clinical diagnosis, the overall performance of these tools compared with non-cancer patients is lower. The molecular complexity of cancer pain is regarded as a mixed pain state as it involves inflammatory, neuropathic and cancer-specific pain mechanisms. Therefore rigorous assessment irrespective of the stage is mandatory to identify neuropathic components; this is crucial to choose the appropriate treatment strategies.4 NCP is a multistep process, which explains the presence of diverse clinical presentations. This is why combination treatment options are necessary for effective pain relief.8 Specific drugs for neuropathic pain including gabapentinoids (gabapentin, pregabalin), antidepressants (tricyclic antidepressants, duloxetine, venlafaxine) may be effective for some patients, but not all.8,9 Therefore NCP as such requires complex management using pharmacological as well as non-pharmacological and psychological approaches.4

References