Role of the sympathetic nervous system in pain

Gordon Stewart
Ajit Panickar

Abstract
The involvement of the sympathetic nervous system in chronic pain conditions has been well described and recognized for over a century. However, the exact mechanism of the relationship has not been fully explained. In certain chronic pain conditions (e.g. complex regional pain syndrome (CRPS)), the presence of sympathetic signs forms part of the diagnostic criteria.

Typical management will involve a multidisciplinary approach, including physical, pharmacological, and psychological therapies. Interventional techniques such as sympathetic blocks can also be used; however evidence of efficacy for many treatments remains poor.

Keywords Chronic pain; CRPS; neurostimulation; sympathetic blockade; sympathetic pain

Royal College of Anaesthetists CPD matrix: 2E03

History
Although sympathetic features had been noted in chronic pain in the late 18th century (Sir Percival Pott) and early 19th century (Alexander Denmark), it was not described in detail until the American Civil War in 1864, when Silas Weir Mitchell described his experience treating the victims of gunshot wounds to the limbs. Mitchell named this condition ‘causalgia’ (from Greek words for burning and pain) to describe burning pain, swelling, changes in skin colour and temperature, and nail changes.

Later in the 1940s J.A. Evans coined the term ‘reflex sympathetic dystrophy’ after observing the success of sympathetic blockade. Both terms have now been replaced by the umbrella term of ‘complex regional pain syndrome’ at a meeting of the International Association for the Study of Pain (IASP) in Florida in 1993.

Pathophysiology
Sympathetic and somatosensory nerves lie in close anatomical proximity in both the peripheral and central nervous systems. Damage resulting from injury or illness can induce a state of pain that is perpetuated by sympathetic activity. The precise pathophysiology of sympathetically maintained pain (SMP) is still fiercely debated.

Pathophysiological concepts thought to be involved in SMP include:
- chemical coupling between sympathetic and nociceptive neurons
- the development of α-adrenoceptor supersensitivity in skin with release of inflammatory mediators
- direct coupling of sympathetic and sensory pathways in the dorsal root ganglion
- central sensitization within the spinal cord
- abnormal cortical neuronal plasticity causing major changes in limb perception.

These hypotheses are not mutually exclusive and it is likely that combinations of pathophysiological processes are responsible for the clinical features seen. There may also be genetic predisposition to developing SMP with an association with HLA II DR15. Some studies showing increased plasma extravasation in response to substance P, and exaggerated neurogenic vasodilatation in the normal limbs of CRPS patients when compared to healthy individuals.

Diagnosis
Diagnostic criteria for CRPS were developed IASP1 in 1993. These original criteria did not account for motor or trophic changes, and were subsequently updated in 2003 at an international consensus meeting in Budapest. The revised criteria are listed in Figure 1. Being the product of consensus, they are sensitive but lack specificity. There is no reliable diagnostic test. The diagnosis of SMP and CRPS is a clinical one.

Patients may undergo formal investigations in order to exclude other significant pathology (e.g. vascular, musculoskeletal and other neuropathic conditions).

Investigations may provide supportive evidence of CRPS or SMP and these include: infrared thermography (may demonstrate temperature asymmetry), quantitative sweat tests (show sudomotor changes), radiographs (identify osteoporosis and altered bone density), technetium bone scans (altered uptake), and MRI (soft tissue changes).

‘Diagnostic’ sympathetic blocks have been used historically to identify SMP. However this practice is unreliable with many false-positive and false-negative results.

Treatment
Many treatment options exist for the management of SMP. These include physical, medical and psychological methods, with variable results observed. No single therapy has shown consistent

Gordon Stewart MBChB MRCP FRCA is a Specialty Registrar (ST7) in Anaesthesia at Glasgow Royal Infirmary, UK. Conflicts of interest: none declared.

Ajit Panickar MBBS MRCP (UK) FRCA is a Consultant in Anaesthesia and Pain Medicine at Victoria Infirmary, Glasgow, UK. Conflicts of interest: Dr Panickar has received a fee from Grunenthal for speaking at an educational meeting for general practitioners. This was donated to charity in its entirety.
benefit in all cases of SMP, and so it is essential that management takes place in a multidisciplinary setting. Treatment should be individualized and patient centred. In all cases the goal of therapy should be functional rehabilitation.

**Physical therapy** includes a range of activities with a focus on functional rehabilitation. Patient education and graded exposure to activity are offered. This can be achieved through exercise, graded motor imagery techniques (GMI), relaxation and massage. Although good-quality evidence is lacking, physiotherapy is generally considered as an essential component of care. GMI, which includes left/right discrimination, explicit motor imagery and mirror therapy, has the most evidence. These techniques focus on re-education of sensory and motor centres within the central nervous system (CNS). Despite recent interest in GMI, no conclusions can be made on which patients are most likely to benefit and how best to apply the techniques.3

**Psychological therapies**
Chronic pain and emotional distress with psychological dysfunction often co-exist, and one may predispose to the other. Psychological support can be provided formally by healthcare professionals, and specialist psychologists, but can also be provided informally by family, friends and employers. A thorough knowledge of the patient’s bio-psychosocial circumstances will inform the level of support required. Particular problems amenable to specialist intervention include learned avoidance behaviour, low motivation, depression, and abnormal health beliefs. Strategies may include cognitive behavioural therapy, mindfulness, relaxation and imagery therapies.

**Drug therapy**
Although many patients with SMP will be on combination pharmacotherapy, there remains a lack of evidence for the many agents commonly in use. Drugs with proven benefit in neuropathic pain have been advocated in CRPS, however their use in this context has yet to be fully established by way of clinical trials. Gabapentin and pregabalin are anti-convulsants which have been shown to reduce pain intensity, hyperaesthesia, and allodynia in neuropathic pain. Tricyclic antidepressants such as amitriptyline, and selective serotonin and noradrenaline reuptake inhibitors (SNRIs) such a duloxetine, also have evidence of benefit in neuropathic pain conditions.

Ketamine has remained a drug therapy of interest due to its action as an N-methyl-D-aspartate (NMDA) receptor antagonist, and a potential to modify the central sensitization seen in sympathetically maintained pain states. A recent systematic review details nine small case series all reporting effectiveness of ketamine in treating CRPS.4 However as there are no large, well-designed trials, no definitive recommendation can yet be made.

Topical therapies such as lidocaine plaster, and capsaicin, are popular with patients and have a low systemic side effect profile. A systematic review concluded that lidocaine plaster can reduce pain intensity in neuropathic pain conditions, but insufficient evidence exists to recommend it as a first-line agent.5 Evidence for topical capsaicin in CRPS is scarce with one case report of successful treatment within 6 weeks.6

Some evidence exists for intravenous (IV) bisphosphonates if given early. They may reduce pain intensity and reduce the incidence of CRPS-associated osteoporosis. A single 60-mg dose of IV pamidronate is recommended in the Royal College of Physicians guidelines of 2012 for suitable patients with CRPS of less than 6 months’ duration.

Other drug therapies include corticosteroids, and free radical scavengers, although insufficient evidence exists to make any clinically valid conclusions.

A recent study has evaluated the use of intravenous immunoglobulin therapy, showing a reduction of pain intensity after 6–19 days, with no adverse effects.7 Although promising, the study was small with only 13 patients and larger studies are necessary.

Although many patients will have trials of the above therapies, they are also commonly prescribed simple analgesics such as paracetamol, and non-steroidal anti-inflammatory drugs, as

---

**Figure 1 Revised diagnostic criteria for complex regional pain syndrome (CRPS) and categories of symptoms and signs.**

**Budapest revised criteria for CRPS**
- **Criterion 1**: Continuing pain, which is disproportionate to any inciting event
- **Criterion 2**: At least one SYMPTOM from three of the categories opposite
- **Criterion 3**: At least one SIGN from two of the categories opposite at time of evaluation
- **Criterion 4**: No other diagnosis that might account for signs and symptoms

**Categories of symptoms and signs in CRPS**
- **SENSORY**: Alloodynia, hyperalgesia
- **VASOMOTOR**: Temperature asymmetry, skin colour change or asymmetry
- **SUDOMOTOR**: Oedema, sweating change or asymmetry
- **MOTOR/TROPHIC**: Decreased range of movement, weakness, dystonia, tremor, skin/hair/nail changes

---

**ANAESTHESIA AND INTENSIVE CARE MEDICINE 14:12 525 © 2013 Elsevier Ltd. All rights reserved.**
well as weak and strong opioids. The use of strong opioids in
treatment of chronic non-cancer pain remains an area of much
debate and controversy, however in carefully selected cases
opioids can be effective in neuropathic pain states.

**Sympathetic blockade**

Many sympathetically maintained pain conditions have an
accessible anatomical site for interventional sympathetic
blockade. A summary of potential targets is given in Table 1.
Intravenous regional sympathetic blockade with guanethedine
or phentolamine also has some evidence of efficacy in small
trials.8

Substantial evidence for these techniques is lacking, however
the practice remains popular among pain clinicians. In the cor-
rect setting (i.e. multidisciplinary with experienced practi-
tioners), these techniques can be used as an adjunct to achieve
temporary functional improvement.

**Neurostimulation**

Transcutaneous electrical nerve stimulation (TENS) can be of
benefit to patients with CRPS, other neuropathic pain conditions
or in somatic pain. A very low side effect profile, and its low
complexity, makes this technique a sensible early therapeutic
option.

Beyond transcutaneous electrical stimulation, neuro-
stimulation techniques become more advanced and invasive.
Spinal cord stimulators have good-quality evidence of benefit
in CRPS and in certain chronic neuropathic pain conditions
(e.g. failed back surgery syndrome).9 A 5-year follow-up study
of CRPS patients in a randomized trial described significant
improvement in perceived pain, although the effect diminished
over time.10

Stimulators can be sited either neurosurgically, or via an
epidural technique. A small but significant risk of adverse
events exist notably accidental dural puncture, and CNS

<table>
<thead>
<tr>
<th>Summary of sympathetic blocks</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Block</strong></td>
</tr>
<tr>
<td>Sympathetic ganglia</td>
</tr>
<tr>
<td>Sphenopalatine Ganglion</td>
</tr>
<tr>
<td>Stellate ganglion</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Ganglion impar</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Autonomic plexus</td>
</tr>
<tr>
<td>Coeliac plexus</td>
</tr>
<tr>
<td>Hypogastric plexus</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Sympathetic chain</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
</tbody>
</table>
| CRPS, complex regional pain syndrome.
| a Complications such as bleeding, infection, direct nerve injury, inadvertent intravenous injection and local anaesthetic toxicity are a plausible risk with all techniques and have not been mentioned specifically. |

Table 1
infection. A multidisciplinary team assessment is essential to ensure individual patients are appropriate candidates for a stimulator. It is usual practice for a device to be trialled, with the inserted electrodes connected to an external system, before permanent implantation is performed. This strategy helps ensure that only patients with beneficial results have a permanent system with the associated cost and potential risks. Despite its expense, this can be a cost-effective treatment where other therapies have failed, especially if the patient can return to normal activities.

REFERENCES


FURTHER READING