ARTICLE

Complex regional pain syndrome

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SUMMARY

Complex regional pain syndrome is an uncommon chronic pain condition. It develops spontaneously or following an injury.

The features are limb pain, allodynia, hypersensitivity, hyperalgesia, abnormalities of the vasomotor, sudomotor and motor systems, and trophic changes, with reduced use of the affected limb. The diagnosis is clinical and one of exclusion.

The emphasis of therapy is graded rehabilitation and movement of the limb with physiotherapy and occupational therapy. Psychological therapies should be offered if a patient is making no or slow progress in the acute phase, and to all patients in the chronic phase as depression can occur.

The goal of pharmacotherapy is to assist functional improvement. The early phase may be managed with simple analgesia. Antineuropathic drugs including tricyclic antidepressants and antiepileptic drugs may be added. Other treatments with some evidence of effectiveness include corticosteroids, calcitonin and bisphosphonates.

Vitamin C has been used for primary prevention after wrist fracture and upper and lower limb surgery. There is no evidence that it is effective for treating established complex regional pain syndrome.

Introduction

Complex regional pain syndrome is a painful debilitating condition in a limb. It is associated with abnormalities in skin, bone, and the autonomic, sensory and motor nerves.[1,2]

In complex regional pain syndrome type I there is no evidence of nerve damage. This was formerly called reflex sympathetic dystrophy or Sudeck's atrophy. In complex regional pain syndrome type II there is a history of nerve injury. This was formerly called causalgia.

The syndrome occurs spontaneously or is triggered by injury, such as a strain or sprain, a distal fracture or surgery.[1-3] The upper limb is affected more in adults[2] and the lower limb in children.[4] Usually, the pain is out of proportion to any preceding injury.

Epidemiology

Complex regional pain syndrome accounts for approximately 2–5% of adult and up to 20% of paediatric pain clinic patients. The prevalence in Australia is unknown. It affects females more, in a 3.5:1 ratio in adults[2] and 9:1 in children.[4] The prevalence is highest in Caucasians.[3]

Pathophysiology

The pathophysiology of complex regional pain syndrome is debated and there are possibly multiple mechanisms. Suggestions include inflammation and changes in the brain and sympathetic, peripheral and spinal nervous systems, aggravated by immobility.[1,5-7] Research using functional imaging and electroencephalogram mapping is providing more information, with demonstrated topographical shrinkage in cortical activation, for example of the hand region of the motor cortex, and reduction in the size of the somatosensory homunculus (reduced face-to-hand distance).[5,6] Altered neurological processing occurs with development of neglect, spatial perception change and reduced two-point discrimination.[5,6,8]

Clinical features

The clinical course varies. The pain spreads regionally, beyond a single dermatome, for example from hand to forearm. It is commonly described as burning, shooting or sharp. Patients may be unable to tolerate clothes, bedding, wind or water touching their limb (allodynia). Sleep disturbance and avoiding using the limb are common. A 'hot florid' phase of variable duration usually occurs early with a red, warm, sweaty limb, later progressing to a 'blue cold' atrophic phase. Some patients have the blue cold phase from the outset.[6] Swelling occurs in both phases and fluctuates (mild to extreme). Motor manifestations vary and include stiffness and impaired coordination.[6]

The natural history of complex regional pain syndrome is variable. Some patients' symptoms spontaneously resolve in weeks or months, while other patients have persistent pain and allodynia with

stiffness. A few develop a wasted, contractured, shiny limb.[1-3,9] The prognosis in children is better, as more patients achieve full recovery.[4] Relapses[3] and spread to other limbs can occur.[9]

Diagnosis

The diagnosis is clinical.[1] Investigations are only performed to exclude other diagnoses. Diagnostic features include symptoms and signs that have no other cause, in several categories:

- sensory – allodynia (pain sensed with a non-painful stimulus), hyperalgesia (increased pain sensed with a painful stimulus), hyperaesthesia (increased sensitivity felt with a stimulus)
- vasomotor – changes in skin colour and temperature
- sudomotor – oedema, sweating
- motor – weakness, tremor, dystonia
- trophic – changes in skin, hair or nails.

Prevention

Complex regional pain syndrome can be difficult to treat, so there is interest in preventing it or recognising it early in its clinical course. Earlier multimodal intervention may positively influence outcome. While there is limited evidence about prevention, providing good analgesia after trauma or surgery seems appropriate. There is no physical or psychological profile to identify which patients warrant prophylactic intervention in the setting of limb injury or surgery and immobilisation (splinting/casting), or early treatment for complex regional pain syndrome.

There is some evidence that vitamin C 500–1000 mg daily for 50 days reduces complex regional pain syndrome after wrist fracture and limb surgery (4 studies, 1065 patients).[10] Perioperatively, strategies used for primary prevention and prevention of recurrence include:

- regional, sympathetic or epidural block or infusion
- corticosteroids
- non-steroidal anti-inflammatory drugs (NSAIDs) such as cyclo-oxygenase (COX-2) inhibitors
- clonidine, ketamine or lignocaine infusions.

To date, none of these perioperative strategies has specific clinical trial evidence to support their use.

When to refer

Clinicians are often faced with the quandary of an anxious, distressed patient seeking a diagnosis or physical explanation for their ongoing pain that can then be repaired or treated. Other investigations may be required to rule out infection, non-union, or a missed bony or soft tissue injury.

The instruction to move a painful (often swollen) limb is counterintuitive to the first-aid principle to immobilise and rest following acute injury. Patients may not accept this advice.

If complex regional pain syndrome is suspected, then early referral is encouraged. High initial pain scores, high levels of emotional distress, anxiety or catastrophisation, and moderate to high opioid requirements beyond the first week are possible flags. As spontaneous remission can occur, patients can be given encouragement.

Treatment

There is little evidence to guide therapy because of the difficulties in studying specific interventions in complex regional pain syndrome.[1-3,11] These difficulties include the need for multidisciplinary treatments, limited numbers of patients, differing diagnostic criteria, the varying nature and duration of the clinical manifestations, and knowing whether recovery is due to treatment or spontaneous remission.

Treatments are often based on expert opinion and what works in other neuropathic pain conditions. It is difficult to prepare guidelines[1,11] or advice[12] for treatment because of the limited number of trials. One approach is a mixture of several drugs and other interventions according to the symptomatology and comorbidities present. Having an agreed treatment plan can help with management.

Physical therapy

Physiotherapists and occupational therapists have a key role. Standard treatment includes desensitisation, contrast baths (ice-cold vs hot-warm water immersion), hydrotherapy, graded exercise/strengthening, gradual increase in weight loading of the limb (by using weights, or pushing down on a set of bathroom scales), sensory re-education/exposure therapy (placing limb in sand, use of tactile gloves and texture boxes) and oedema control (compressive garments).[1] The patient must move, exercise and reintegrate the limb into normal everyday activity.[11]

Graded motor imagery has evidence supporting its use.[6,8] This involves phased 'brain retraining' with left–right (laterality) discrimination training (photographs and mobile apps to identify limb side, improving accuracy and speed of response), proceeding to imagined and then mirrored movements.[7,13-16] Transcutaneous electrical stimulation has been used but without an evidence base to support it.

Psychological therapy

Psychological sequelae, including depression, anxiety, fear of movement and fear of harm/re-injury, are common due to ongoing pain, physical, emotional

and social losses.[16-19] Patient education about the pathophysiology, the negative effects of disuse and the reasons for resuming function, and the interplay of psychological and behavioural factors are important as for any chronic pain condition.[18] Physical therapists with experience in complex regional pain syndrome routinely use psychological strategies and psychoeducation incorporated with the physical intervention. If the patient fails to make progress (acute phase) or once the condition becomes chronic, a formal psychological assessment should be offered. Then, specific therapies can be considered and tailored for the patient as part of a 'whole person' approach.[1,20] These include learning, mindfulness and relaxation techniques, the adoption of active rather than passive coping strategies, cognitive behavioural therapy and, recently, acceptance and commitment therapy. Cognitive behavioural therapy (six sessions) in children has been added to outpatient physiotherapy, with positive effect.[1]

The psychological interventions attempt to address any external factors or incentives that can positively or negatively influence the patient's problems. For example, claims for compensation may add to the patient's stress.

Drug therapy

In addition to the lack of evidence for most treatments, few drugs have an indication for complex regional pain syndrome. The lack of subsidy by the Pharmaceutical Benefits Scheme (PBS) can result in significant out-of-pocket expenses for the patients.

The Table includes analgesics typically used in the community as first- to fourth-line therapies. Simple analgesia is used to address pain and stiffness to facilitate movement during exercise and to limit the use of opioids. Paracetamol has no specific evidence in complex regional pain syndrome, but is used.[1] NSAIDs, including COX-2 inhibitors, are used, particularly when oedema is present, alone[1] or added to paracetamol. Typically, opioids or tramadol have been started for acute pain management after the initial injury. Tramadol's efficacy is via noradrenaline and serotonin reuptake inhibition (parent compound) and opioid effects (metabolite). The former mechanism results in antineuropathic as well as somatic benefits. Tramadol is used second- to third-line, in some countries, in preference to opioids. The ongoing use of opioids when complex regional pain syndrome is suspected or formally diagnosed is controversial. Generally, if the use of an opioid assists physical gains or compliance with therapy, then continued use is acceptable as third- or fourth-line therapy.

Corticosteroids can be considered in the early inflammatory phase.[1,21] The optimal time for starting these and the duration of treatment is uncertain. A prednisolone dose of 30 mg/day can be gradually tapered off, but there is no evidence for any regimen.

As there is some evidence for vitamin C in prevention, it has been used as treatment early in the syndrome. However, there is no evidence to support this practice.

Patients may be prescribed an antidepressant often in combination with an antiepileptic drug, usually one of the gabapentinoids: gabapentin or pregabalin (Table). For sleep disturbance, tricyclic antidepressants are favoured. Giving a higher dose of gabapentin or pregabalin at night can also be tried.

Gabapentin is not subsidised by the PBS for this indication. Although it is more expensive, pregabalin is subsidised if other therapies for neuropathic pain have failed. A head-to-head trial of gabapentin and pregabalin in neuropathic pain has not been done. Their adverse effect profiles are similar (dizziness, altered concentration, sedation). Pregabalin has twice-daily dosing, while gabapentin is given three times a day.

When tricyclic antidepressants or gabapentinoids are poorly tolerated, rotation within the same drug class can be considered (e.g. amitriptyline to nortriptyline, or gabapentin to pregabalin) or to alternative antidepressants or antiepileptics, but there is no reported experience with these strategies (Table). If the patient has severe anxiety or depression and cannot tolerate tricyclics in antidepressant doses, or if their pain or mood is not improving, then alternative antidepressant drugs such as duloxetine can be considered. However, the evidence to support their use for complex regional pain syndrome is lacking. The dose of tricyclics used in complex regional pain syndrome is frequently too low to be effective for treating coexisting depression. Serotonin syndrome is a risk if doses of antidepressants are being escalated and the patient is also taking moderate to maximal doses of tramadol.

Antiepileptic drugs have been used with varying levels of supporting evidence (Table). The off-label use of newer antiepileptic drugs, such as topiramate, for complex regional pain syndrome is expensive.

Specialist interventions

If the patient fails to improve on optimised therapy, then the pain specialist will consider other interventions. Clonidine has low-grade evidence of effectiveness, but is cheap and is often used in Australia. Dimethyl sulfoxide cream has some evidence to support its use, but it is an organic solvent that can irritate the skin. It is available depending on the capacity of local hospital and community pharmacies. Other gels and creams are available but have

Table **Commonly used drugs for complex regional pain syndrome and levels of evidence** [1] *

Drug	When used	Dose	Evidence
Paracetamol	First-line analgesic	Usual doses but capped at the recommended maximum daily dose in chronic use	None
NSAIDs including COX-2 inhibitors	First-line analgesic particularly if muscle stiffness, oedema	Take regularly vs when required before physical therapy or exercise	Limited
Opioids	Third- to fourth-line in early phase. Use is 'acceptable' if it permits physical gain (opioids may have been started to manage initial injury) Controversial use in later phase so possibly restrict to short-term use for pain crisis	Avoid high doses and long-term use due to risks of death, dependency, tolerance, overdose, opioid-induced hyperalgesia, and long-term adverse effects	Debated
Tramadol	Second- to third-line	Usual doses; immediate and slow release	None
Antiepileptics	Either alone or in combination with antidepressants		
gabapentin		100–1200 mg 3 times daily	Level 4
pregabalin		25–300 mg 2 times daily	None
carbamazepine (oxcarbazepine)		200 mg 3 times daily	Level 2
phenytoin		Usual doses	None
others: • topiramate (appetite suppression can be a significant advantage) • valproate • lamotrigine		Usual doses	Anecdotal use, no trial evidence
Antidepressants	Either alone or in combination with antiepileptics		
Tricyclics • amitriptyline • nortriptyline	Particularly useful if sleep disturbance	Start low e.g. 10–25 mg and up-titrate to 1–2 mg/kg	None
SSRI/SNRI • paroxetine • duloxetine • venlafaxine • citalopram	May be preferable in overweight, somnolent patients or if unable to tolerate tricyclic antidepressants or have prominent anxiety/depression	Usual doses	Not studied

NSAIDs non-steroidal anti-inflammatory drugs COX cyclo-oxygenase
SSRI selective serotonin reuptake inhibitor SNRI serotonin and noradrenaline reuptake inhibitor

* According to National Health and Medical Research Council hierarchy

limited or no supporting evidence. These are often anecdotally effective for patients unable to tolerate oral drugs. They include single or combination drugs such as topical NSAIDs (available over the counter), local anaesthetics, ketamine (e.g. 2.5–5%) or clonidine (e.g. 0.01%) and amitriptyline/nortriptyline (e.g. 2%) gels. Capsaicin may be tried, but it is messy and painful and therefore invariably unpopular with patients. Patches of local anaesthetic, clonidine or capsaicin have also been used but are not always available.

Various regimens of ketamine and lignocaine infusions have become widely used, but patients need to be hospitalised and there is uncertainty regarding the optimal dose, duration and frequency of these treatments.

Calcitonin and bisphosphonates can reduce bone resorption and may have other actions. There is

evidence to support their use in complex regional pain syndrome.[1]

Invasive interventions

Sympathetic blockade (stellate ganglion block and lumbar sympathetic block) has been used extensively despite limited supporting evidence. The blocks are offered generally for the hot florid phase and for the blue cold phase, if there is prominent oedema. It is also unclear whether permanent sympathectomy is better than repeated temporary local anaesthetic blocks. Epidural block (providing sympathetic and somatic block) is sometimes used for inpatient treatment.

Implantable pumps (for lower limb) and stimulators (for lower or upper limb) have been used in severe or resistant complex regional pain syndrome. They require a rigorous selection process, significant expertise to insert, adjustment and ongoing supervision. The evidence to support these interventions is limited and they need further evaluation. The same is true for the experimental use of anti-inflammatories and immunomodulators in complex regional pain syndrome. Infliximab, intravenous immunoglobulin and thalidomide have been tried in very small case series.

Conclusion

Complex regional pain syndrome is an unusual neuropathic pain condition. Current therapy involves actual and simulated limb use facilitated by multimodal intervention and polypharmacy with drugs for neuropathic and inflammatory pain. Research is further delineating the pathophysiology and may eventually lead to the development of targeted therapy. Good-quality trials to support the use of drugs and other interventions are necessary. ◀

Conflict of interest: none declared

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