



■ REVIEW ARTICLE

Complex regional pain syndrome with special emphasis on the knee

G. S. E. Dowd,
R. Hussein,
V. Khanduja,
A. J. Ordman

*From the Royal Free
Hospital, London,
England*

Complex regional pain syndrome is characterised by an exaggerated response to injury in a limb with intense prolonged pain, vasomotor disturbance, delayed functional recovery and trophic changes. This review describes the current knowledge of the condition and outlines the methods of treatment available with particular emphasis on the knee.

Historical considerations

Complex regional pain syndrome has had many synonyms over the years, including causalgia, Sudeck's atrophy, post-traumatic dystrophy, shoulder-hand syndrome, algodystrophy, algoneurodystrophy, reflex neurovascular dystrophy and reflex sympathetic dystrophy, reflecting the confusion surrounding this condition. Latterly, the disorder has been termed complex regional pain syndrome types I and II by the International Association for the Study of Pain.^{1,2} The condition was noted by Sir James Paget (1814-1899) who described aspects of causalgia³ and later by Mitchell et al,³ and Schutzer and Gossling.⁴ In 1900, Sudeck⁵ described a troublesome painful condition in a limb, associated with swelling, stiffness and vasomotor instability after trauma.

Definition

A simple and comprehensive definition has been presented by Schutzer and Gossling,⁴ which describes an exaggerated response to injury of a limb, manifested by intense prolonged pain, vasomotor disturbances, delayed functional recovery and trophic changes.

The various terminologies describing this condition have been encompassed by the International Association for the Study of Pain^{1,2} into a single term, complex regional pain syndrome, to accommodate the various presentations, postulated pathophysiology and anatomical distribution. The syndrome is said to be present when a noxious stimulus, which may be minor, causes an excessive response, with regional pain and sensory changes associated with the findings of a sympathetic dis-

order, manifested by changes in temperature, discoloration of the skin, swelling and sudomotor activity.⁶ Trophic changes occur in the skin, nails and bone. Motor changes may present as impaired voluntary movements, fine or coarse tremors and dystonic posturing or movements.

Two types of complex regional pain syndrome have been recognised.^{1,2,6} Type I is not associated with a specific nerve injury and does not follow the anatomical distribution of a peripheral nerve. Type II, although having a similar group of symptoms and signs to those of type I, is associated with a specific nerve injury and probably correlates with the syndromes previously termed causalgia.^{1,2,6}

Although complex regional pain syndrome occurs in both the upper and lower limbs, response to treatment in the latter is less favourable, which has led to the suggestion that it is a discrete entity of the lower limb.⁷

Pathophysiology

The definite aetiology of complex regional pain syndrome is unclear and many theories have been postulated.

1) It has been suggested that there is an abnormal increase in the activity of the sympathetic nervous system after a stimulus.⁶⁻⁹ This may be a result of increased activity in the nerves, failure to modify the response centrally, perhaps due to reduced sensory input from the injured limb, or an increase in the peripheral catecholamine receptor sensitivity or injury-mediated hypersensitivity at the target organs to sympathetic discharge.⁶⁻⁹

2) Formation of artificial synapses may occur between nerve fibres in the dorsal-root ganglion after a peripheral injury with result-

■ G. S. E. Dowd, MD,
MCh(Orth), FRCS, Consultant
Orthopaedic Surgeon
■ R. Hussein, MSc, FRCS G,
FRCS(Trauma & Orth), Knee
Fellow
■ V. Khanduja, MRCS, MSc,
FRCS(Trauma & Orth), Knee
Fellow
Department of Trauma &
Orthopaedics
■ A. J. Ordman, FRCA,
Consultant Anaesthetist and
Pain Specialist
Department of Anaesthesia and
Pain Management
The Royal Free Hospital,
Hampstead, London NW3 2QG,
UK.

Correspondence should be sent
to Mr R. Hussein;
e-mail: ramihussein2@aol.com

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ant shunting of impulses between sympathetic and sensory fibres.^{6,7}

3) Direct nerve injury may cause an abnormal electrical discharge, which may stimulate sensory nerves directly, or cause an imbalance in release of transmitter giving rise to an abnormal response.^{6,7}

4) There may be an exaggerated local inflammatory response to injury resulting in disruption of the autoregulation of blood flow, giving rise to the classic phases of complex regional pain syndrome.^{7,9}

5) There may be affliction of the central and peripheral nervous system with variable involvement of somatosensory, sympathetic, neurovascular, neuro-inflammatory and somatomotor systems.^{10,11}

6) Psychological input has been suggested although it seems to be secondary, a result of the syndrome rather than a cause.^{6,8,9}

As always, many theories regarding the aetiology raise the question of whether it is a single entity and whether there are other predisposing factors, perhaps genetic,⁹ resulting in such an abnormal response to a precipitating factor.

The initiator

Complex regional pain syndrome is initiated by a noxious stimulus. This may be a trivial injury,^{4,5} such as a simple blow to the knee, which would be expected to heal readily, or a surgical procedure. A common trigger in the knee seems to be derangement or injury to the patellofemoral joint, which some authors believe is always involved when complex regional pain syndrome affects the knee.^{8,12} Arthroscopic surgical procedures of the knee seem to be a common precipitating cause although it may be present, undiagnosed, before surgery.^{8,13} A minor sprain of a collateral ligament during arthroscopy, or injury to a branch of the saphenous nerve during meniscal repair, may provide the initiating stimulus.⁶ Concern has been expressed that diagnostic arthroscopy for evaluating pain in the knee is seldom justified, since this can be a cause of, or exacerbate, pre-existing complex regional pain syndrome, particularly if evaluation can be completed using other techniques, such as MRI.^{8,13}

Incidence

The precise incidence and prevalence of complex regional pain syndrome are not known. It is thought that the incidence of severe complex regional pain syndrome is low,⁹ although milder forms are more common after fractures and surgical trauma. It has been estimated that some degree of the syndrome will occur in one of 2000 accidents involving a limb.¹² It occurs in children as well as in adults,¹⁴ but seems to favour the lower limb in children and the upper limb in adults.^{14,15} In the knee the overall incidence is higher in adults, affecting females predominantly.^{8,16}

Its occurrence after total knee replacement is said to be uncommon^{8,17} although it should be included in the differ-

ential diagnosis when evaluating a painful stiff total knee replacement.^{17,18} Nevertheless, some authors have proposed that mild forms occur quite commonly after this procedure, with stiffness being a possible long-term sequel.⁹

Symptoms and signs

Symptoms typically begin soon after the injury although in some cases they may take a few weeks to become apparent. The expression of the symptoms and signs may vary between patients. An exaggerated pain response, burning in nature, with intolerance to cold, is the classical presentation. The pain is usually non-anatomical in distribution, although in type II it can be along the distribution of the involved nerve.^{6,7} Patients often complain of a continuous deep pain, which they localise to the bone. In addition, allodynia is present, so that light touch provokes an unpleasant sensation or causes moderate to severe pain. There may also be spontaneous pain like an electric-shock in the limb. Movement, dependency and touch aggravate symptoms. Oedema is commonly seen and may be subtle with a loss of skin creases, or more obvious. Patients are often disbelieved by clinicians because the symptoms and signs do not appear to follow an accepted anatomical distribution. Traditionally, three stages have been defined.^{7,8}

1) Acute, occurring up to three months from the injury. The limb is warm, red or mauve. There is swelling and an altered pattern of sweating with palmar or plantar hyperhidrosis, hyperaesthesia and stiffness of the joint, but with no effusion or fixed contracture.

2) Dystrophic, at three to six months after the injury. The limb is cool and cyanotic with induration. Hyperaesthesia is present and fixed contractures occur.

3) Atrophic, occurring after six months. The skin becomes hairless and loses its creases. Contractures prevail and the changes become permanent.

Somatomotor disturbances also occur, manifested by weakness of all the muscles in the region, impairment of fine, accurate movements, increased physiological tremor, intention tremor, postural dystonias and disuse.

More recently, complex regional pain syndrome has been described as being a biphasic condition,⁹ with an acute stage of up to six months, and thereafter a chronic stage similar to the atrophic stage in the traditional model. This has practical implications, since the early stage is thought to be more amenable to treatment than the chronic condition.

The classical clinical presentation and progression are often absent in complex regional pain syndrome of the knee⁸ and patellofemoral involvement may produce reduced patellar mobility, patellar and retinacular tenderness and hypersensitivity.⁸

Differential diagnosis

Diagnosis is based on the clinical picture, the response to sympathetic blockade and the exclusion of other diagnoses such as post-operative infection, nerve injury⁶ and the formation of a neuroma, particularly related to the saphen-

ous nerve in the knee, vascular insufficiency, neoplasms, stress fractures and missed intra-articular disorders. Causes of referred pain must be considered and investigated, including nerve compression due to spinal pathology or peripheral entrapment.¹⁹ Pelvic disorders and occult osteoarthritis of the hip should be ruled out in patients with knee symptoms. Metabolic and inflammatory disorders as well as neuropathies must also be considered.^{16,19}

Diagnosis

Complex regional pain syndrome must be applied only as a specific clinical diagnosis and not used to label patients with an unsatisfactory surgical outcome.

The diagnosis is predominantly clinical⁷ and should always be considered given the variability of presentation. The full blood count, erythrocyte sedimentation rate (ESR), fasting blood sugar, and serum calcium levels should be measured and thyroid function tests performed to exclude systemic causes of pain.^{16,19}

Plain radiography shows normal findings in the early stages,¹⁶ but is beneficial in excluding concomitant or other pathology such as a stress fracture.⁷ After three months, patchy subchondral osteopenia is usually present and with involvement of the knee, the characteristic finding is osteopenia of the patella and medial femoral condyle on the skyline view.^{7,8} In the late stages profound bone demineralisation occurs.⁹ It has been suggested that the more diffuse classical osteopenia is less common in complex regional pain syndrome of the knee⁸ although a degree of osteopenia is always present.¹² The radiological findings are typically not seen in children.¹⁴

Technetium-99 bone scanning is very sensitive but not specific.^{6,8} The most common finding is an increased uptake of the isotope in each phase of the bone scan.¹⁵ At 30 seconds, the arterial phase illustrates hyperaemia and arteriovenous shunting in the affected limb. At three minutes, the isotope demonstrates the propensity for fluid to leak from the capillaries to form oedema. At three hours, the isotope is concentrated in periarticular bone demonstrating the accelerated bone metabolism. Increased uptake in the knee can be seen as an increase in periarticular uptake, diffuse uptake about the knee, or increased uptake limited to the patella.¹² Decreased uptake in the acute setting has also been reported, particularly in children,^{6,15} and normal bone scans particularly in the late stages are not uncommon.^{9,12}

Thermography with or without cold challenge is useful. In complex regional pain syndrome, considerable asymmetry of skin temperature is created during controlled thermoregulation. This feature can be used as a supplementary bedside test to assist in the diagnosis, with a high sensitivity and specificity (76% and 93%, respectively).²⁰

Electromyographic and nerve-conduction studies can help to identify nerve damage, entrapment and neuropathies.¹⁹

MRI is useful in ruling out other disorders which may be acting as a constant stimulus,⁸ such as a missed meniscal tear. It may also show bone-marrow oedema,⁹ soft-tissue changes and occult fractures. However, the MRI findings may be normal.²¹

Sympathetic blockade is helpful in the diagnosis of complex regional pain syndrome.^{6,8,22} If there is no relief from pain for the duration of a complete sympathetic block, then the diagnosis of complex regional pain syndrome is less likely. A documented increase in the skin temperature of 1°C to 3°C confirms the success of the sympathetic nerve block. There are various ways of achieving it.⁶ This can be by intravenous delivery of an alpha-blocking agent such as phentolamine, intravenous regional blockade with guanethidine, conducted like a Bier's block, differential spinal blockade, epidural blockade and local anaesthetic blockade of the paravertebral lumbar sympathetic chain. The last is the most effective since it avoids blocking the sensory and motor nerves.

Treatment

There are three areas of treatment, namely physical therapy, the use of pharmacological agents and sympathetic blockade either by injections or operative intervention.⁶

Physical therapy

Physiotherapy. This is considered to be essential and should be the first line of treatment. Gentle physiotherapy is directed towards controlling oedema by massage, preventing joint contractures and re-establishing voluntary motor control. In the knee, this should include gentle mobilisation of the patella. Aggressive therapy should be avoided since patients with complex regional pain syndrome have an exaggerated response to painful and non-painful stimuli,^{6,7} and any pain caused may exacerbate the condition. Physiotherapy should progress slowly through range of movement and strengthening exercises, with the avoidance of pain and forced passive movements. Splinting may be helpful to avoid contractures,⁴ but should be removed for regular exercise periods since immobility may worsen the condition. Cryotherapy should also be avoided because of the cold intolerance while moist heat may be helpful.⁶ Personality confrontations should be avoided. A good rapport will help with the patient's compliance in continuing treatment.¹⁶

Ogilvie-Harris and Roscoe²³ studied the response to physiotherapy, which included transcutaneous electrical nerve stimulation, in 19 patients with complex regional pain syndrome of the knee. All received non-steroidal anti-inflammatory drugs (NSAIDs) and analgesics in addition. Of seven patients who presented within six months, five responded to conservative measures and two went on to have a sympathetic block. In nine patients with late complex regional pain syndrome, only two responded reasonably well to physiotherapy. In three patients in a separate group classified as having a post-operative syndrome, only one seemed to have benefited from physiotherapy.

It appears that there is a better response to these measures in early complex regional pain syndrome of the knee.^{8,12,23,24}

Mirror visual feedback. This has been used in the early stages of the type I syndrome.²⁵ Its effect is based on the finding that visual input from a moving, unaffected limb re-establishes the pain-free relationship between sensory feedback and motor execution in the affected limb. In a series of eight patients with type I complex regional pain syndrome, three with early and two with intermediate disease at up to one year had a good result from using mirror visual feedback, which had been implemented after failure of other treatments including analgesia, physiotherapy and sympathetic blocks. Three patients with chronic disease did not benefit.²⁵

Transcutaneous electrical nerve stimulation. This may be helpful although its efficacy is not clear.^{4,6,7} It has been used in both adults and children,^{4,14} with a variable outcome. Some patients have experienced good long-term relief from a single treatment. Most require several sessions.⁴ In a study evaluating the management of complex regional pain syndrome in children, 61 patients received transcutaneous electrical nerve stimulation. In four there was complete resolution, in 27 improvement, in 25 no effect and in five the symptoms were made worse.¹⁴

Acupuncture and electroacupuncture. Acupuncture and electroacupuncture have been used. In a series of 20 patients with complex regional pain syndrome after hand injuries, acupuncture needles were placed on the affected limb, connected to a stimulator and a monophasic electrical pulse passed for 20 to 30 minutes.²⁶ The electroacupuncture sessions were repeated five to ten times. A total of 14 patients experienced marked permanent improvement and a further four had some improvement. No complications or worsening of symptoms were noted.

Pharmacological agents

These are used to modify the sympathetic and non-sympathetic symptoms and include the use of simple analgesics, NSAIDs, steroids,⁴ narcotics, anti-neuropathic drugs such as gabapentin,⁷ calcium metabolism modulators such as bisphosphonates²⁷ and calcitonin,²⁸ propranolol and nifedipine. Control of pain is essential for successful treatment and a combination of drugs, such as a tricyclic antidepressant, gabapentin and a strong opiate may be needed to achieve this. Most of these medications are not familiar to the orthopaedic surgeon^{6,7} and since early treatment is thought to have a favourable outcome, particularly in the upper limb,^{7,12,23} early referral to a pain management team is paramount.

Sympathetic blockade

Failure to respond to non-invasive methods should be followed by the use of sympathetic blocking agents.⁸ Regional intravenous guanethidine blockade has been used extensively in the United Kingdom. Its efficacy is unclear,⁷ with contradictory reports appearing in the literature.^{29,30}

Combinations of lidocaine and corticosteroids have also been used for regional blockade.⁵ Central blocks include differential spinal blockade,⁶ epidural spinal blockade⁶ and paravertebral sympathetic blockade, which is the preferred method.⁶

Lumbar surgical sympathectomy should be the procedure of last resort and is used in cases in which sympathetic blockade has provided only short-term relief.⁶ This has shown to be quite effective in complex regional pain syndrome type II, particularly in the lower limb.³¹

Cooper and DeLee⁸ and Cooper, DeLee and Ramamurthy³² studied the response to treatment of complex regional pain syndrome of the knee using continuous epidural anaesthesia in 14 patients. All had a painful patellofemoral joint and had undergone conservative treatment including physiotherapy, which had failed. After confirming the diagnosis with a sympathetic block, the patients were admitted to hospital and an indwelling lumbar epidural catheter was inserted to establish a continuous epidural block using bupivacaine, providing initial complete epidural anaesthesia with sympathetic, sensory and motor block. A continuous passive-movement regime was begun and once the patient had regained movement, the bupivacaine was changed to narcotic epidural agents to provide relief from pain without a motor block, allowing the patient to mobilise. During the epidural block, manipulation was performed if the patient failed to achieve an arc of flexion measuring 90°, as well as muscle stimulation, alternating hot and cold applications, and psychological evaluation. The epidural agents were reduced over a few days depending on the response. At a mean follow-up of 32 months (7 to 48), 11 patients had complete resolution of symptoms with full activity, two had partial improvement and one had no relief. In the three failed cases, symptoms had been present for more than six months before the epidural block.

Katz and Hungerford¹² described the outcome in the knee after lumbar sympathetic block or sympathectomy in 36 patients. Injuries or surgery around the patellofemoral joint were related to the onset in 23 of these patients. Most had severe long-standing involvement. Of the series, 21 patients had a good result after lumbar sympathetic block and 15 were fair. However, 32 had recurrence of their symptoms and 23 of these agreed to a sympathectomy, with a good result in 15 and a fair outcome in eight. Sympathetic blockade or sympathectomy in patients within one year of the onset of symptoms resulted in a better response compared with those with a longer duration of symptoms before such intervention.

O'Brien et al¹³ reported the outcome of repeated outpatient lumbar sympathetic blockade in 60 patients with complex regional pain syndrome of the knee. Of these, 55 had relief from symptoms after a mean of nine blocks (1 to 30). The most common cause of the syndrome in the group was arthroscopic procedures. The authors also noted that those with a persistent anatomical lesion, such as definable

loss of cartilage, had a worse outcome than those without such a finding.

Operative intervention

Stimulation of the spinal cord has been used with some efficacy.^{24,33} Electrodes are introduced into the epidural space and connected to an external pulse generator. If effective, the generator is permanently implanted in the subcutaneous tissue. In a series of 12 patients with early and intermediate complex regional pain syndrome not responding to treatment, epidural spinal cord stimulation was used with an excellent response in eight patients and a good improvement in the remaining four.³³

Cooper and DeLee⁸ proposed a treatment algorithm for the knee based on their experience. In early cases a trial of conservative management is undertaken. This includes the use of NSAIDs, alternatively immersing the limb in hot and cold soaks, muscle stimulation, intensive pain-free physiotherapy and progressive weight-bearing. If there is no adequate response to this trial of treatment or the patient presents with progressive symptoms for more than six weeks, a sympathetic block is carried out to confirm the diagnosis and to provide treatment. If the symptoms return, inpatient treatment with an indwelling lumbar epidural catheter is undertaken to establish a continuous epidural block, as described previously.

Prognosis

There is overall agreement that initiating treatment in the early stages carries a better prognosis compared with that in those diagnosed late, which are more refractory to treatment.^{4-6,12,22,23,28,31} This may be explained by the difficulty in managing chronic syndromes and because irreversible changes are more likely to occur with time.⁶ In the knee, restricted movement is very common¹² and patellofemoral pain may follow stiffness. Patella baja and changes in the mechanics of the tibiofemoral joint may occur, leading to chondral degeneration.⁶ Most authors state that when early diagnosis and treatment are implemented, within six to 12 months, an overall good outcome is the rule.^{5,12,23,28} This is particularly true in the knee.¹² In a series of 36 patients undergoing sympathetic blockade for complex regional pain syndrome affecting the knee, the ten treated within a year from the onset of symptoms did significantly better than those with symptoms of more than a year before the commencement of sympathetic blockade.¹² Most authors agree that spontaneous resolution can occur in the early stages,^{24,28} while permanent residual symptoms may be a feature in chronic cases.⁵

Summary

Complex regional pain syndrome is a difficult condition to manage and presents with certain features which should alert the orthopaedic surgeon. Presentation in the lower limb is less characteristic and diagnosing the condition in the knee after surgery can be difficult since symptoms can

be confused with those related to the surgery, and investigations such as MRI, may not be helpful. When the knee is affected, the patellofemoral joint is always involved. It is sometimes difficult to establish whether complex regional pain syndrome was present before the operation or whether surgery precipitated its presentation. It is generally accepted that early diagnosis and initiation of treatment are important factors in achieving success.^{4-6,12,22,23,28,31} The upper limbs are generally more amenable to treatment than the lower⁷ and children fare better than adults, with physiotherapy being quite effective in the former.¹⁴ Some authorities have advised avoidance of diagnostic surgery, particularly diagnostic knee arthroscopy, if it is possible to gain adequate information by other non-invasive methods such as MRI.⁸ Surgery should be avoided in the presence of complex regional pain syndrome, but if it is necessary, the condition should be treated first by physiotherapy and perhaps by a continuous epidural local anaesthetic block, sufficient to cause sympathetic blockade, for a few days peri-operatively.

It should be noted that complex regional pain syndrome is a specific diagnosis, which needs to be made on clinical grounds and should not be used as a label for all unexplained pain or adverse surgical outcomes. More research is required to improve the understanding of this unpleasant condition.

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