PEER REVIEWED

A case of complex regional pain syndrome post fracture

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This section focuses on the immediate management and investigation of an acute pain presentation in general practice.

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Jane is a 39-year-old woman who suffered a nondisplaced fracture of her left ankle two months ago. This occurred following a simple fall with no other injuries sustained. She attended hospital promptly for treatment and was managed conservatively with a cast. During the first five weeks following the injury she presented to you, her GP, complaining of increasing pain and swelling from the left ankle. You referred her to the fracture clinic at the hospital orthopaedic department where they decided to remove the cast early. Repeat x-ray of the ankle was performed, which revealed normal bone alignment and good healing of the fracture. The ankle was, however, noted to be erythematous, hot and swollen. Investigations were performed and included full blood count, measurement of urea, electrolyte and C-reactive protein levels, blood culture, D-dimer test and lower limb venous ultrasound scan. Inflammatory markers were normal and no evidence of infection or deep vein thrombosis was found.

The patient was discharged from the orthopaedic department as there was felt to be no ongoing surgical issue. However, nine weeks after her fracture Jane returns to you with severe pain affecting her left leg from the mid-calf down to her toes on the side of the fracture. Her left leg is swollen, erythematous and the skin has taken on a shiny appearance. She has tried taking regular paracetamol, ibuprofen and over-the-counter paracetamol 500 mg combined with codeine 10 mg with no benefit.

What else would you want to know from this patient's history and examination?

Answer: You want to know more about the pain Jane is experiencing, including the character of the pain and any neuropathic descriptors, such as 'burning' or 'shooting', and if there is any increased sensitivity to painful stimuli (hyperalgesia) or pain from normally nonpainful stimuli (allodynia). You should enquire about additional symptoms, such as reduced movement or ability to weight bear, dystonia, changes in colour or temperature of the limb, or alterations in appearance and quality of the skin, hair or nails.

Subsequent to this it is helpful to gain an understanding of the impact this is having on Jane's day to day life – what degree of functional limitation is she experiencing as a result, and does the pain impact on her sleep or mood?

What is the differential diagnosis?

Answer: The differential diagnosis in cases such as this is extensive but includes the following:[1]

- complex regional pain syndrome
- other post-traumatic neuropathic pain
- infection (bone, soft tissue, joint or skin)
- orthopaedic malfixation
- joint instability
- arthritis or arthrosis
- bone or soft tissue injury (including stress fracture, instability or ligament damage)

1. Budapest criteria for diagnosing complex regional pain syndrome[2]

The patient must fulfill criteria A, B, C and D to be given a diagnosis of complex regional pain syndrome.

A. The patient has continuing pain, which is disproportionate to the inciting event.
B. The patient has at least one sign (you can observe on examination) in two or more categories listed below.
C. The patient reports at least one symptom (at some point) in three or more categories listed below.
D. No other diagnosis can better explain the signs and symptoms.

Categories

- Sensory. Allodynia (to light touch, temperature sensation and/or deep somatic pressure and/or joint movement) and/or hyperalgesia (to pinprick). Hyperaesthesia also counts as a symptom.
- Vasomotor. Temperature asymmetry (if observed must be >1°C) and/or skin colour changes and/or skin colour asymmetry.
- Sudomotor/oedema. Oedema and/or sweating changes and/or sweating asymmetry.
- Motor/trophic. Decreased range of motion and/or motor dysfunction (weakness, tremor, dystonia) and/or trophic changes (hair/nail/skin).

- compartment syndrome
- neural injury (peripheral nerve damage, including compression or entrapment neuropathy, or central nervous system or spinal lesions)
- arterial insufficiency (usually after preceding trauma, atherosclerosis in the elderly or thrombangiitis obliterans [Burger's disease])
- Raynaud's disease
- lymphatic or venous obstruction
- erythromelalgia
- self-harm.

You examine the patient and note that her left leg is warmer compared with the right, there is increased hair growth on the left leg, the toe nails are cracked and the foot is sweaty. Sensory examination reveals that she has allodynia and severe hyperalgesia in a non-dermatomal distribution from the mid-calf downwards. You make a diagnosis of complex regional pain syndrome (CRPS).

What are the criteria necessary to make a diagnosis of CRPS?
Answer: A diagnosis of CRPS is based on the Budapest Criteria[1] (see Box 1).[2]

There are two types of CRPS: type 1 and type 2. In CRPS type 1, a discrete nerve lesion cannot be identified, whereas in CRPS type 2 it can be identified.[3] CRPS type 1 is by far the most common diagnosis.

Who is most at risk of developing CRPS?
Answer: The following are risk factors for the development of CRPS:[3-5]

- female sex
- increasing age (but can occur in children)
- fracture – this is the most common preceding event (but can occur following dislocation, surgery or even minor injury)
- upper limb – more commonly affected than lower limb
- use of ACE inhibitors.

There is no evidence that pre-existing adverse psychology contributes to the development of CRPS.[3] However, the presence of 'yellow flags' (see Box 2) may contribute to a more protracted, difficult clinical course with more disability.

Can CRPS be prevented?
Answer: Good quality postoperative analgesia and regional anaesthesia for peripheral limb surgery or fracture repair are important. There is good quality evidence that vitamin C 500 mg per day taken from the day of fracture and continued for six weeks results in a significant reduction in the incidence of CRPS.[7] Despite the simplicity, safety and low cost involved with this intervention it is rarely used in practice.

What are the mechanisms underlying CRPS?
Answer: There is an incomplete understanding of the mechanisms that lead to the development of CRPS. Current theories are based on the following outlined below.[2]

2. Yellow flags for people with complex regional pain syndrome[6]

- Iatrogenic factors (i.e. previous negative experiences with healthcare professionals)
- Involved in litigation, which is affecting willingness to progress with treatment (note that this is not the case for all patients involved in litigation)
- Poor coping strategies (e.g. ongoing 'guarding' of the limb despite education)
- Overuse of appliances
- Distress
- Anxiety/depression
- Lack of willingness to set goals
- Passive in treatment sessions
- Inappropriate beliefs despite education
- Negative family influences

Adapted from Main et al. BMJ 2002; 325: 534-537.[6]

- The role of a neuroinflammatory process. There is evidence of increased expression of inflammatory markers (such as interleukin [IL]-8 and tumour necrosis factor alpha) and neuroinflammatory mediators (such as substance P) in the affected limb along with suppression of anti-inflammatory cytokines such as IL-4 and IL-10.
- Sympathetic dysregulation is believed to be partly responsible for the colour and temperature changes of the affected limb. However, some researchers have questioned the significance of the sympathetic nervous system as a primary source of imbalance in the development of CRPS.[2]
- Central sensitisation is important in the maintenance of the pain long term.
- Cortical reorganisation and altered perception of the affected limb has been shown in functional MRI studies.
- CRPS could be related to small fibre neurone damage.
- Microvascular circulatory disturbance creating an 'ischaemia-reperfusion' type injury and the localised build up of reactive oxygen species.

Table. Pain-modulating drugs for complex regional pain syndrome

Class	Drug	Dosing	Side effects	Other information
Gabapentinoids (one may be better tolerated than the other)	Gabapentin	Usually start 300 mg at night, increase after 3 days to twice daily then after another 3 days to 300 mg three times daily Can continue to increase slowly by 300 mg at a time. Maximum dose 1200 mg three times daily If elderly or with renal impairment start 100 mg instead of 300 mg	Common side effects include dizziness, drowsiness, weight gain and peripheral oedema	Benefit may not be seen at low doses so need to increase dose as tolerated until benefit without unacceptable side effects Not available on the PBS for pain
	Pregabalin	Usually start 75 mg at night, increase after 3 days to twice daily Can continue to increase slowly by 75 mg at a time. Often will require 150 mg twice daily or above for benefit. Maximum dose 300 mg twice daily If elderly or with renal impairment start 25 mg instead of 75 mg	Common side effects include dizziness, drowsiness, headaches, weight gain and peripheral oedema	Benefit may not be seen at low doses so need to increase dose as tolerated until benefit without unacceptable side effects PBS listed (authority required) for neuropathic pain, must be refractory to treatment with other drugs
Tricyclic antidepressants	Amitriptyline*	Start 10 mg (5 mg in the elderly) at 6 pm and titrate dose up as tolerated	Side effects include postural hypotension, balance problems, confusion, seizures, dry mouth, urinary retention, constipation	Benefit may not be seen at low doses so need to increase dose as tolerated until benefit without unacceptable side effects
	Nortriptyline*	Start 10 mg (5 mg in the elderly) per day at 6 pm and titrate dose up as tolerated	As above, but probably less side effects than amitriptyline	Possibly safer than amitriptyline in the elderly
SNRIs	Duloxetine*	Start 30 mg per day and increase after one week to 60 mg Maximum dose 120 mg/day	Common side effects include dry mouth, dizziness, headaches, nausea, drowsiness	
	Others: venlafaxine* and mirtazapine* occasionally used	Initiation of venlafaxine usually by a specialist. Mirtazapine may also improve sleep		
Weak opioid and SNRI	Tramadol	Immediate-release preparation: 50 to 100 mg as required for severe pain Slow-release preparation: start 50 mg twice daily and increase as needed/tolerated. Maximum dose 400 mg/day	Common side effects include dizziness, nausea, constipation, dry mouth, headaches, drowsiness	Use with caution with tricyclic antidepressants, SNRIs, SSRIs and MAOIs as risk of serotonergic syndrome

Abbreviations: MAOI = monoamine oxidase inhibitor; SNRI = serotonin and noradrenaline reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor.
* Used off-label for general neuropathic pain.

What are the initial steps in the management of this condition?

Answer: There is little good quality evidence on the treatments available for CRPS,[1] so initial management is usually based on using anti-neuropathic medications to try to reduce the pain and helping the patient to engage in a rehabilitation program aimed at desensitisation and improving function.[1] It is important to rule out other causes by referring the patient to appropriate specialist services (e.g. rheumatologist, orthopaedic specialist). Early referral of the patient to a pain specialist and specialist physiotherapy and/or occupational therapy is vital to try to reduce the risk and impact of chronicity.[1,2]

Pain-modulating drugs that may be initiated by the GP include those drugs traditionally used as anticonvulsants (primarily the gabapentinoids) and antidepressants (tricyclic antidepressants and serotonin and noradrenaline reuptake inhibitors [off-label uses]). Tramadol may also be used for severe pain, as it is a weak opioid with some antineuropathic action. The Table presents more information on these drugs.

Other treatments that may be initiated by pain specialists or physiotherapy/occupational therapist for CRPS include:[1,2,8]

- bisphosphonates – particularly in acute phase (specialist initiation, in some centres only, either as intravenous infusion of pamidronate or alendronate, or oral alendronate [all off-label uses for CRPS])
- ketamine (off-label use)
- intravenous lignocaine (off-label use)
- lignocaine patches (off-label use)
- short pulsed corticosteroid therapy
- desensitisation therapy
- graded motor imagery and mirror therapy
- psychology (e.g. cognitive behavioural therapy)
- transcutaneous electrical nerve stimulation
- strong opioids (with caution)
- spinal cord stimulation (rarely).

The treatment of CRPS is often challenging, and early diagnosis and specialist treatment should be considered essential.

Outcome: Jane found that the antineuropathic medications helped reduce the severity of her pain, allowing her to better engage with a specialist physiotherapist. She was referred to a specialist pain clinic and six months later, following a multidisciplinary, multimodal approach to the management of her pain she found that although she had a level of persisting pain, her function and mood were improved. PMT

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