



COMPLEX REGIONAL PAIN SYNDROME FOLLOWING SPINAL DISEASES AND SURGERIES

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ABSTRACT

Complex regional pain syndrome (CRPS) impairs the patient's active life and his/her psychological state due to reductions in functional movements, severe pain, and muscle atrophy. Fractures and surgical operations are important risk factors for CRPS, and several studies reported incidences of CRPS following surgical procedures to the upper or lower limb. CRPS can also be seen after spinal diseases and surgeries, yet the literature includes only limited number of studies in this area and there are not enough works considering incidence of CRPS following spinal problems. While early diagnosis and appropriate treatment of CRPS in acute period are very important for prevention of chronic symptoms (including allodynia, swelling, muscular atrophy, osteoporosis and contracture), clinicians need to be aware that the spinal problems may cause CRPS. The aim of this review is to emphasize the possibility of CRPS development after spinal diseases or surgeries and strongly argue that the diagnosis of CRPS following spinal problems must be considered by clinicians.

Keywords: Complex regional pain syndrome, spinal disease, spinal surgery, spinal cord injury, spinal tumor

INTRODUCTION

Complex regional pain syndrome (CRPS) impairs the patient's active life and his/her psychological state due to reductions in functional movements, severe pain and muscle atrophy. CRPS is characterised by a severe, generally not well-tolerated, pain that usually involves the extremities. The most significant complaints are severe pain with edema and other vasomotor and motor symptoms, such as temperature and/or skin colour asymmetry, dystonia and tremor. Although current medical treatments often target acute symptoms, CRPS can also become chronic, lasting for months or years, accompanied with other symptoms due to irregularities in the sympathetic nervous system. Even though CRPS can be characterised as a chronic neurological disease, it is generally caused by a triggering trauma, such as fractures, surgeries or even minor injuries.

Acute and Chronic CRPS

CRPS may be categorised into two: CRPS type 1 may occur without nerve lesions and CRPS type 2 is associated with nerve lesions caused by a triggering trauma^(1,2). Even in the absence of nerve damage, a triggering trauma and subsequent flared posttraumatic inflammation may be observed. The progression of this syndrome is variable, but the clinical presentation is often similar in both groups: in the acute period, common

features include the five main signs of inflammation, namely, pain, edema, erythema, changes in skin temperature/colour and dysfunction⁽²⁾. In fact, the transient features of CRPS may be observed more commonly than most clinicians realise and CRPS may even occur after minor limb injuries. As CRPS becomes chronic, symptoms can evolve, and allodynia, sweating, dystonia and muscle atrophy may occur during the disease course. During this period, symptoms may appear exaggerated and disproportionate in degree and duration with respect to the triggering event, and chronic symptoms of CRPS can no longer be explained by the initial trauma.

Vasomotor dysfunction is common in patients with CRPS. While the affected limb is generally warmer than the healthy limb at earlier stages, it becomes colder in the later phases of the syndrome⁽²⁾. While red and hot lesions are observed in the acute phase, if the patient is not treated appropriately, the drop in the skin temperature of the affected area can result in cold lesions in the chronic phase.

Importance of Early Treatment of CRPS

In patients with CRPS, symptoms tend to begin during the first month following trauma and/or immobilisation of the extremity⁽³⁾; physical problems may begin approximately 2 years after disease onset^(4,5). Since CRPS has no known evidence-based effective treatment, approximately 15% of the



patients experience unbearable pain. If CRPS is not properly treated in the acute period (3–6 months from onset), tendons may shorten and fibrosis may develop⁽⁶⁾; thus, contractures may occur very quickly.

In chronic CRPS, symptoms can lead to complete disruption of normal daily activities due to severe pain and atrophy in the affected limb. This may lead to excessive use and abuse of drugs for CRPS treatment^(3,7), and drug side effects may be observed. In particular, long-term and high-dose usage of opioids may cause severe problems due to tolerance, dependence, immune suppression and dysfunction in the endocrine system. Long-term usage of opioids may also cause hyperalgesia⁽⁸⁾. Respiratory suppression due to opioid overdose may result in death. Delayed and insufficient treatment may increase the risks of complete deterioration in daily activities, major depression and suicide⁽⁷⁾. If treatment options are ineffective, amputation may be required; physical and psychological problems in CRPS may become so severe that clinical teams encountered patients who requested limb amputation⁽¹⁾. However, even after such a drastic intervention, phantom pain (77% of the cases)⁽⁹⁾ and CRPS recurrence in the remaining extremity (24% of the cases)⁽¹⁰⁾ remain as potential risks.

As presented above, early treatment of CRPS is very important in preventing long-term symptoms (allodynia, muscular atrophy, etc.); thus, clinicians must start appropriate treatment protocols without any delay when early diagnosis of CRPS is possible⁽¹¹⁾. Unfortunately, CRPS is not easy to diagnose.

Early Diagnosis of CRPS

Early diagnosis of CRPS may prevent long-term complications and sequelae, including muscle atrophy, osteoporosis, joint stiffness, tendon shortening and contracture, which weaken the patient's active life by reducing his/her functional movements. A major problem with the diagnosis of CRPS is that symptoms can mimic other diseases. Diagnosis relies on clinical findings; unfortunately, a gold standard and objective diagnostic test for CRPS is not yet established. CRPS is diagnosed clinically using the diagnostic criteria of the International Association for the Study of Pain (*Budapest Diagnostic Criteria for CRPS*)^(7,12).

Table 1 lists some of the diagnostic signals that should be considered⁽³⁾. During differential diagnosis, especially for complex cases, imaging tests (including magnetic resonance imaging and computed tomography) may be performed to exclude other possible diseases. Plain film may also be used, except in extreme cases (Sudeck's atrophy).

Electromyography and nerve conduction studies may help assess the presence of nerve injury and muscle fibre loss. Three-phase bone scintigraphy may detect trophic changes of the bone. Local anaesthetic sympathetic blocks are commonly used for diagnostic purposes. If a patient has a good response to a diagnostic sympathetic block with local anaesthetic, sympathetic denervation through radiofrequency ablation can be offered for therapeutic purposes.

Since CRPS symptoms are similar to that of other diseases, patients often undergo evaluation by multiple specialists

before the final diagnosis is confirmed, and this may lead to significant delays in treatment. These delays may also increase the risk of the disease becoming chronic and may lead to serious economic losses for the patient.

Risk Factors for CRPS and Incidence of CRPS after Fractures/ Surgeries

Common risk factors for CRPS are listed in Table 2⁽¹³⁻¹⁷⁾. According to de Mos et al.⁽¹⁴⁾, women are three times more affected by

Table 1. Differential diagnosis⁽³⁾

| |
|--|
| • Infection (bone, soft tissue, joint or skin) |
| • Orthopaedic mal-fixation |
| • Joint instability |
| • Arthritis or arthrosis |
| • Bone or soft tissue injury (including stress fracture, instability or ligament damage) |
| • Compartment syndrome |
| • Neural injury (peripheral nerve damage, including compression or entrapment, or central nervous system or spinal lesions), or neuropathy (such as from diabetes, alcohol misuse) |
| • Thoracic outlet syndrome (due to nerve or vascular compression) |
| • Arterial insufficiency [usually after preceding trauma, atherosclerosis in older people or thrombangitis obliterans (Burger's disease)] |
| • Raynaud's disease |
| • Lymphatic or venous obstruction |
| • Brachial neuritis or plexitis (Parsonage-Turner syndrome or neuralgic amyotrophy) |
| • Erythromelalgia (may include all limbs) |
| • Self-harm |

Table 2. Risk factors for CRPS⁽¹³⁻¹⁷⁾

| Risk factors | |
|--|--|
| Age | The most common age is 61-70 years |
| Gender | Female: Male 2:1 |
| Localization | Upper-lower limb 3:2 |
| Menopause | |
| Osteoporosis | |
| Asthma | |
| ACE inhibitory treatment | Affects the neuroinflammatory mechanism that causes CRPS through substance P and bradykinin metabolism |
| Migraine | |
| Smoking | Poor prognosis in smoking |
| CRPS: Complex regional pain syndrome, ACE: Angiotensin-converting enzyme | |

CPRS than men. Individuals aged 61–70 years are most commonly affected, and the risk is highest in postmenopausal women. According to the same study, the upper limb is affected more frequently than the lower limb, and the most common trigger events are fractures, accounting for 44% of the cases. As shown in Table 3⁽¹⁸⁻²³⁾ and Table 4⁽²³⁻³⁴⁾, several studies reported a high incidence of CRPS, especially after distal radius fracture (32.2%), Colles' fracture (36.7%), tibial fracture (30%) and shoulder (11.1%) and tibial (31%) surgeries⁽¹⁾. Unfortunately, CPRS-related complications following orthopaedic surgeries may negatively affect the postoperative healing process, and the syndrome may lead to serious long-term problems, including unbearable pain and immobilisation.

While there is a strong evidence of CRPS incidence following fractures and surgical operations, there is little prior work on the incidence of CRPS following spinal surgeries. Most studies

indicating potential presence of CRPS following spinal diseases and surgeries are based on case studies.

METHODS

This study aimed to present a review of the literature on CRPS occurrence following spinal problems and surgeries to improve physicians' awareness of this. For this review, we combed the published literature for studies of patients who developed CPRS after three main spinal problems, including degenerated/herniated disc surgeries, spinal cord injury (SCI) and spinal cord tumor. Published studies were grouped under these three categories and further investigated according to the type of CRPS (1 or 2), disease origin and grade, type of surgeries prior to CRPS onset, disease course, therapies following diagnosis of CRPS and age (ranged from 22 to 69 years) and sex of the

Table 3. Reported incidence of CRPS following fractures of the upper and lower limb⁽¹⁾

| Region | Antecedent event | Study | Incidence |
|-------------------|---|--|----------------|
| Upper limb | Distal radius fracture | Jellad et al. 2014 ⁽¹⁸⁾ | 32.1% (26:61) |
| | | Dijkstra et al. 2003 ⁽¹⁹⁾ | 1.1% (1:87) |
| | Colles' fracture | Bickerstaff and Kanis 1994 ⁽²⁰⁾ | 28.1% (77:197) |
| | | Atkins et al. 1990 ⁽²¹⁾ | 36.7% (22:38) |
| | | Beerthuisen et al. 2020 ⁽²²⁾ | 7.9% (18:209) |
| Scaphoid fracture | Beerthuisen et al. 2020 ⁽²²⁾ | 0% (0:27) | |
| Lower limb | Tibial fracture | Sarangi et al. 1993 ⁽²³⁾ | 30% (9:21) |
| | Ankle fracture | Beerthuisen et al. 2020 ⁽²²⁾ | 15.2% (21:117) |
| | Fifth metatarsal fracture | Beerthuisen et al. 2020 ⁽²²⁾ | 2.9% (3:100) |

CRPS: Complex regional pain syndrome

Table 4. Reported incidence of CRPS following surgical procedure of the upper and lower limb⁽¹⁾

| Region | Operation | Study | Incidence |
|------------|-----------------------|---------------------------------------|----------------|
| Upper limb | Shoulder | Chalmers et al. 2014 ⁽²⁴⁾ | 11.1% (1:8) |
| | | Arndt et al. 2012 ⁽²⁵⁾ | 3.0% (3:97) |
| | | Gonzalez et al. 2011 ⁽²⁶⁾ | 0.9% (35:3975) |
| | | Bishop et al. 2005 ⁽²⁷⁾ | 1.3% (1:79) |
| | | Borgeat et al. 2001 ⁽²⁸⁾ | 1.0% (5:516) |
| | Carpal tunnel release | Shinya et al. 1995 ⁽²⁹⁾ | 1.9% (2:105) |
| | | Lichtman et al. 1979 ⁽³⁰⁾ | 5.0% (5:95) |
| | | MacDonald et al. 1978 ⁽³¹⁾ | 2.2% (4:182) |
| | | Lilly and Stem 2010 ⁽³²⁾ | 2.0% (1:49) |
| | | Bulstrode et al. 2005 ⁽³³⁾ | 2.4% (6:247) |
| Lower limb | Tibial | Sarangi et al. 1993 ⁽²³⁾ | 31% (9:20) |
| | Ankle and foot | Rewhorn et al. 2014 ⁽³⁴⁾ | 4.4% (17:373) |

CRPS: Complex regional pain syndrome

Table 5. CRPS cases following spinal diseases and spinal surgeries

| Case study | Patient Age/Gender CRPS type | Spinal disease or spinal surgery | Treatment | Progress |
|--------------------------------------|------------------------------|---|--|--|
| Plancarte 1997 ⁽³⁵⁾ | 39/F CRPS2 | Postoperative automated laser discectomy | Chemical lumbar sympathectomy | Chemical sympathectomy resulted in resolution of the pain syndrome |
| Fish 2005 ⁽³⁶⁾ | 65/M CRPS2 | Post-lumbar surgery (sacroiliac fusion) | Subsequently three sympathetic blocks and conservative treatment | The patient had dramatic improvement after treatment and no recurrence of the CRPS developed |
| Chae et al. 2009 ⁽³⁸⁾ | 40/M CRPS2 | Postoperative micro-discectomy for lumbar spine herniation (L4-5) | Spinal cord stimulator | VAS score and tingling sensation improved, but tremor, weakness and hyperesthesia still existed |
| Weisz et al. 2010 ⁽⁴¹⁾ | 39/M | Cervical disc protrusion and posterior foraminotomy (C5-6, C6-7) | Conservative treatments (opioids, tricyclics and hypnotics) | Postoperative 34. month less intense, several features of CRPS were still evident |
| Knoeller et al. 2011 ⁽³⁷⁾ | 31/F | Implantation of an artificial disc (L4/5 segment) | CT-guided sympathetic block | Second week of treatment pain, allodynia, swelling regressed, only slight sensory disturbance left |
| Kim et al. 2016 ⁽⁴²⁾ | 22/M | Lumbar herniated intervertebral disc disease (L4-5) | Decompression of herniated disc | Symptoms relieved after operation. VAS score improved |
| Jung et al. 2018 ⁽³⁹⁾ | 31/F | Lumbar discectomy for herniated lumbar disc (L5/S1) | Sacral epiduroscopic laser decompression (SELD) | After second SELD, the patient'S pain markedly decreased. On the second visit in the outpatient clinic, the patient was absent of pain without any other medications |

CRPS: Complex regional pain syndrome, VAS: Visual analog scale, CT: Computed tomography, F: Female, M: Male

patients. We also focused on the reported progress of the disease after therapy.

DISCUSSION

CRPS following Degenerated and Herniated Disc Surgeries

Table 5 lists several studies that report CRPS cases following spinal diseases/procedures. *These studies highlight the possibility*

of CRPS associated with spinal procedures and the importance of early treatment for effective results.

Plancarte and Calvillo⁽³⁵⁾ reported a patient with CRPS type 2, following automated laser discectomy, who presented sympathetically maintained pain and serious disability. The author suggested that CRPS can be associated with spinal procedures, including automated laser percutaneous discectomy. In another case study, Fish presented a patient with CRPS type

2 in a distal extremity associated with an anterior sacroiliac fusion with local bone graft⁽³⁶⁾. Fish argued that CRPS can be associated with spinal procedures and sacroiliac arthrodesis. Both Plancarte and Fish concluded that early intervention is important in long-term resolution of CRPS symptoms.

Knoeller et al.⁽³⁷⁾ reported a case of CRPS 1 of the left leg following lumbar spine surgery (implantation of an artificial disc type in the L4-5 segment) using a midline left-sided retroperitoneal approach via a ventral access (this surgery requires mobilisation of the sympathetic trunk). The report emphasised that diagnosis of CRPS following lumbar spine surgery via a ventral access must be considered a differential diagnosis, and Knoeller et al.⁽³⁷⁾ highlighted the importance of early diagnosis, as early initiation of therapy in CRPS type 1 may improve the progress of a disabling severe disease.

Chae et al.⁽³⁸⁾ reported about CRPS type 2 following a postoperative lumbar spine surgery and pointed out the importance of distinguishing CRPS symptoms from postoperative symptoms. Despite the difficulty in differentiating postoperative syndrome in the lumbar spine from CRPS, they recommended that physicians should consider CRPS as the primary cause of postoperative syndrome in the lumbar spine after orthopaedic surgery, as this may prevent significant losses in time before the start of an effective treatment.

Similarly, Jung et al.⁽³⁹⁾ noted that CRPS-like symptoms can appear after lumbar spinal surgery due to adhesion and inflammation in the epidural space. They reported the case of a 31-year-old patient diagnosed with CRPS type 2 following L5-S1 discectomy. Unfortunately, the patient did not respond to conventional therapies or to spinal cord stimulation for the treatment of CRPS. Consequently, for diagnostic and therapeutic purposes, sacral epiduroscopic laser decompression (SELD) was performed twice 1 month apart. During these procedures, severe adhesion and inflammation at the L4-S1 epidural space were detected. The catheter was placed to perform mechanical adhesiolysis and laser decompression at the herniated intervertebral disc. Three days after the second intervention, the visual analogue scale (VAS) score had improved, and 8

months later, the patient reported complete absence of pain. The authors suggested that if CRPS-like symptoms originating from the lumbar spine cannot be treated by conventional therapy, SELD may be considered an appropriate diagnostic and therapeutic option.

More recently, Wolter et al.⁽⁴⁰⁾ carried out a study to determine the frequency of CRPS following spinal surgery and to investigate the disease course and prognostic factors. 35 patients (18 women and 17 men) who were treated for CRPS (1 or 2) were included in the study. The authors considered the CRPS type, disease origin and grade and type of surgeries prior to CRPS onset. Table 6 reports data regarding six patients (one patient had cervical and five patients had lumbar spine surgery) who had undergone spinal operations just before the onset of CRPS symptoms (median, 5 days; range: 1–14) and had no other trauma preceding the development of CRPS symptoms. As shown, CRPS symptoms following spinal surgery can start very quickly. Consequently, the authors concluded that even if CRPS may occur relatively rarely following spinal surgeries, physicians must be aware of the possibility of CRPS, as early diagnosis and treatment are important to prevent complications.

Most studies about CRPS following spinal problems focus on lumbar disc protrusion and lumbar spinal surgery. In Wolter et al.⁽⁴⁰⁾, only one patient had cervical surgery before CRPS. Weisz et al.⁽⁴¹⁾ reported the case of a 39-year-old patient who had shown CRPS symptoms following cervical spine surgery (posterior foraminotomy at C5–6 and C6–7). Following the surgery, the patient experienced pain, paraesthesia, swelling of the left hand and forearm and increasing inability to use the left hand; as a result, the patient was diagnosed with CRPS. The treatment included opioids, tricyclics and hypnotics on a daily basis, which improved physical features and associated psychological and social problems. 34 months after surgery, symptoms remained less intense; however, several features of CRPS (swelling, paleness and cold and wet skin) were still evident.

Kim et al.⁽⁴²⁾ reported a case of CRPS that was caused by L4–5 herniated intervertebral disc without a history of trauma

Table 6. Data on six patients who had undergone spinal operations shortly before CRPS symptoms (Wolter et al.⁽⁴⁰⁾)

| Study | Patient Age/Gender | Spinal disease/surgery | Time between operation and onset of CRPS |
|------------------------------------|--------------------|---|--|
| Wolter et al. 2012 ⁽⁴⁰⁾ | 57/M | Cervical spine surgery | 1 day |
| | 45/F | Lumbar disc operation (L4-5) | 7 days |
| | 48/M | Dorsoventral spondylodesis (L5-S1) | 14 days |
| | 44/F | Lumbar disc operation (L5-S1) | 14 days |
| | 32/F | Lumbar disc prosthesis (L4-5) | 2 days |
| | 69/M | Hernilaminectomy (L5) and nucleotomy (L4-5 and L5-S1) | 3 days |

CRPS: Complex regional pain syndrome, M: Male, F: Female

or surgery. Percutaneous nucleoplasty was considered as a treatment option for CRPS, after which the symptoms were relieved and the VAS score had improved. While CRPS from a mild herniated intervertebral disc without surgical intervention is even rarer than CRPS after surgery for disc diseases, this possibility should be kept in mind during differential diagnosis.

CRPS in Spinal Cord Injury

Pain is a frequent complication of SCI, and identifying the possible causes of the pain is very important for effective treatment. While neurological problems like stroke and peripheral nerve injuries are known etiological causes of CRPS, several studies reported CRPS also in patients with SCI⁽⁴³⁻⁴⁷⁾. Table 7 summarises the key findings of some of these case studies.

Gellman et al.⁽⁴⁴⁾ studied 60 patients with cervical SCI and identified an overall incidence rate of 10% of CRPS. Lefkoe and Cardenas⁽⁴⁵⁾ presented the case of a 25-year-old tetraplegic male patient with complete traumatic injury of the cervical cord (C6) who presented CRPS. In addition, Lefkoe and Cardenas⁽⁴⁵⁾ pointed out that in patients with SCI, diagnosis of CRPS might be challenging due to the presence of severe pain and other common CRPS complications, such as heterotopic ossification or deep venous thrombosis in SCI patients without CRPS.

Gallien et al.⁽⁴⁶⁾ reported eight CRPS cases in a study of patients with SCI. The study included one female and seven male patients, with a median age of 35. The causes of SCI included gunshot wounds (n=5), car accidents (n=2) and fall (n=1). Five patients had complete SCI, and three patients had incomplete SCI. Four patients were tetraplegic, while four patients were paraplegic. The authors discussed the diagnosis, risk factors and treatment and concluded that, even if this syndrome may be more common in other forms of neurological diseases, such

as stroke, CRPS might also be observed as the main source of pain in patients with SCI.

Sutbeyaz et al.⁽⁴⁷⁾ reported the case of a 49-year-old man with C7 incomplete tetraplegia who presented CRPS type 1 in both upper and lower extremities. The authors emphasised that CRPS type I might be more common in SCI than usually suspected and that tetraplegic patients should be carefully evaluated for the presence of CRPS type I.

CRPS in Spinal Cord Tumor

We have found only one published case of a patient with cervical spinal cord tumor (schwannoma) and CRPS type 2⁽⁴⁸⁾. This 63-year-old patient underwent urgent neurosurgery, and the spinal lesion was excised. At 6 weeks after the procedure, the symptoms had completely disappeared. After 1 year, the patient was still completely asymptomatic.

CONCLUSION

Early diagnosis and proper treatment of acute CRPS are very important in preventing the development of chronic symptoms (including allodynia, swelling, muscular atrophy, osteoporosis and contracture). Clinicians must be aware of the potential scenarios in which patients may develop CRPS. Fractures and surgical operations are critical risk factors for CRPS. *In this review, we emphasised the possibility of CRPS development after spinal diseases and/or surgeries.* While the literature on CRPS following spinal problems consists primarily of small case studies and there are limited data on the incidence of CRPS following spinal problems, there is growing evidence that CRPS may also occur after spinal diseases or surgeries and that the diagnosis of CRPS following spinal problems must be considered by clinicians.

Table 7. CRPS cases following spinal cord injury

| Case study | Patient Age/ Gender | Spinal diseases | CRPS treatment | Progress |
|--|------------------------|---------------------------|---|---|
| Lefkoe and Cardenas 1996 ⁽⁴⁵⁾ | 25/M | C6 complete tetraplegia | Conservative treatments | Conservative treatments resulted in the resolution of the pain syndrome |
| Sutbeyaz et al. 2005 ⁽⁴⁷⁾ | 49/M | C7 incomplete tetraplegia | Conservative treatments | After 6 weeks of treatment, the patient's VAS score for pain had decreased by more than 50% |
| Akkoc et al. 2008 ⁽⁴³⁾ | 55/F | Spinal cord injury | Pulse radiofrequency lumbar sympathectomy | VAS score improved. For 4 months follow-up, the patient did not require opioid |

CRPS: Complex regional pain syndrome, M: Male, F: Female, VAS: Visual analog scale



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Ethics

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