Managing Psychiatric Symptoms in Patients with Complex Regional Pain Syndrome

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ABSTRACT

Complex regional pain syndrome (CRPS) is a rare but debilitating chronic pain condition of the extremities, which often develops after an injury. Its multifactorial pathophysiology includes the immune and nervous systems and, potentially, autoimmune, genetic, and psychological factors. Psychiatric illnesses can be comorbid with CRPS, including mood disorders, anxiety disorders, insomnia, substance use disorder, personality disorders, and somatic symptom disorder. This article discusses these psychiatric symptoms and offers treatment guidance.

KEYWORDS: CRPS, pain, nervous system, immune system, depression, anxiety

Formerly known as reflex sympathetic dystrophy (RSD) or causalgia, complex regional pain syndrome (CRPS) is an uncommon but debilitating chronic pain condition that typically develops in a limb following an injury. It is accompanied by both reported and observed changes in sensation, skin, motor function, and hair or nails. Subjective criteria and lack of confirmatory objective tests have contributed to uncertainty regarding incidence, diagnosis, and classification as a rheumatological or neurological disorder.[1]

An American study of patient data from 1989 to 1990 calculated an incidence of 5.46 cases per 100,000 persons.[2] However, a Dutch study of data from 1996 to 2005 determined overall incidence of 26.2 cases per 100,000 persons, with female patients (particularly postmenopausal) afflicted at least three times more often than male patients.[3] A South Korean study of data from 2011 to 2015 yielded similar results, with an incidence of 29.0 cases per 100,000 persons, with older female patients being predominantly affected.[4]

Developed in the early 1990s, the International Association for the Study of Pain (IASP) diagnostic criteria for CRPS relied on self-reported symptoms.[5] Although sensitive, it lacked specificity and resulted in overdiagnosis.[6] A 2003 meeting in Budapest modified the criteria to improve specificity and diagnostic consistency among clinicians, while maintaining sensitivity.[7] Compared to the original criteria, the modified Budapest criteria maintained sensitivity (0.99 vs. 1.00) and improved specificity (0.68 vs. 0.41), and is the current standard for CRPS diagnosis (Table 1).[6] CRPS is divided into Types 1 or 2, depending on the absence or presence of peripheral nerve injury, respectively.[8] Although diagnosis is a clinical one based on signs and symptoms, adjunctive thermography or bone scintigraphy might be helpful.[8]

PATHOPHYSIOLOGY

The pathophysiology and risk factors for CRPS are unclear but appear to be multifactorial, including nervous and immune system dysfunction, and potentially including autoimmune, genetic, and psychological factors.[8] In the peripheral nervous system, nociceptive pain fibers surrounding the injury become sensitized and coupled to the sympathetic branch of the autonomic nervous system. This promotes continued pain perception, autonomic dysregulation (manifested by sweating and skin temperature changes), and altered pain processing and interpretation in higher central nervous system (CNS) structures, such as the insula and hypothalamus.[9]

The activated immune system releases inflammatory cytokines which cause edema, erythema, pain, and warmth. Chronically high levels of cytokines also promote connective tissue proliferation and contractures, bone demineralization, and hyperalgesia.[9] One study detected CNS autoantibodies in 30 to 40 percent of patients with CRPS, suggesting an autoimmune component.[10] A Dutch family study revealed a possible genetic

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predisposition toward developing chronic pain and CRPS, but this has not been extensively investigated.[11]

RELATIONSHIP WITH PSYCHIATRIC ILLNESS

There is conflicting evidence for a relationship between psychological factors and psychiatric symptoms and CRPS. When symptoms are present, it is uncertain whether they predispose to, predate, or result from CRPS. A retrospective study of 64 patients with CRPS reported a higher prevalence of mental illness compared to individuals with other chronic pain; the most common conditions were adjustment disorder, depression, alcohol or tobacco abuse, and personality disorder.[12] A forensic evaluation of 55 patients with CRPS noted depression in 60 percent, panic attacks in 20 percent, alcohol or other substance abuse in 18 percent, and somatoform disorder symptoms in 42 percent.[13] A prospective study of 152 patients with CRPS detected a higher prevalence of post-traumatic stress disorder (PTSD), compared to individuals with other chronic pain and healthy individuals.[14] Patients with lower baseline anxiety, fear of pain, and perceived disability have better prognoses, compared to patients with higher levels, because the latter group might minimally use the affected limb, paradoxically leading to increased pain and disability.[15] Catastrophic thinking might predispose individuals to CRPS due to a heightened perception of pain.[8] Although no studies assessed the prevalence of insomnia, this is likely present due to the strong bidirectional relationship between chronic pain and insomnia.[16] Furthermore, sleep disturbance can exacerbate pain (especially the following day) or predispose individuals to develop chronic pain.[16]

In contrast, a review concluded that higher quality methodological studies revealed no relationship between psychological factors and CRPS, though stressful life events might increase the risk of developing it.[17] Earlier studies found no association between CRPS and psychological factors. A small retrospective study of 25 patients with RSD found no difference in symptom reporting, illness behavior, psychological distress, or trauma history, compared to subjects with back pain or local neuropathy.[18] A Dutch retrospective case control study compared 186 patients with CRPS to 697 control patients and similarly detected no relationship between CRPS and psychological factors (e.g., anxiety, depression, psychosocial problems).[19] In a small study comparing patients with CRPS (n=25) to those with low back pain (n=25), the prevalence of depression and personality disorder was equally high between groups.[20] This indicated that these psychiatric conditions were not specific to CRPS, but simply indicative of personality traits and coping styles in response to intense chronic pain.[20] A retrospective study compared patients with CRPS (n=76), other chronic pain (n=95), major depression (n=66), and normal controls (n=171) and found that individuals with CRPS were not more psychologically disturbed than those with chronic pain or major depressive disorder, and they tended to underreport or even deny psychological symptoms.[21]

A prospective study assessed for prevalence of psychiatric illness in 103 patients with CRPS of the hand compared to 290 patients with non-CRPS hand limitations, while also evaluating biopsychosocial complexity using INTERMED,[22] a clinical tool that assesses past and present biological, psychological, social, and healthcare factors and disease prognosis using a semi-structured interview or self-assessment.[23] Mood disorders, PTSD, and personality disorders were commonly found in both groups, with no statistically significant difference in prevalence between them.[22] However, INTERMED scores directly correlated to increased risk of psychiatric comorbidities in both groups.[22] This indicates that biopsychosocial impairment contributes to psychiatric comorbidity, rather than CRPS.[22]

Despite the uncertain relationship between psychiatric symptoms and CRPS, there is no consensus or algorithm for treating symptoms that might be present. The recommendations below utilize the current but limited evidence to assist clinicians in managing psychiatric symptoms and pain.

TABLE 1. Modified IASP Budapest criteria[7]

CRITERIA FOR A CLINICAL DIAGNOSIS
Continuing pain, which is disproportionate to any inciting event
Must report at least 1 symptom in 3 of the 4 following categories: • Sensory: Reports of hyperesthesia and/or allodynia • Vasomotor: Reports of temperature asymmetry and/or skin color changes and/or skin color asymmetry • Sudomotor/Edema: Reports of edema and/or sweating changes and/or sweating asymmetry • Motor/Trophic: Reports of decreased range of motion and/or motor dysfunction (weakness, tremor, dystonia) and/or trophic changes (hair, nail, skin)
Must display at least 1 sign at time of evaluation in 2 or more of the following categories: • Sensory: Evidence of hyperalgesia (to pinprick) and/or allodynia (to light touch and/or temperature sensation and/or deep somatic pressure and/or joint movement) • Vasomotor: Evidence of temperature asymmetry (>1°C) and/or skin color changes and/or asymmetry • Sudomotor/Edema: Evidence of edema and/or sweating changes and/or sweating asymmetry • Motor/Trophic: Evidence of decreased range of motion and/or motor dysfunction (weakness, tremor, dystonia) and/or trophic changes (hair, nail, skin)
There is no other diagnosis that better explains the signs and symptoms

IASP: International Association for the Study of Pain

RECOMMENDATIONS

Screening. Clinicians are advised to screen for trauma disorders, mood disorders (especially depression), anxiety disorders, insomnia, and substance use disorders (especially alcohol, opioid, and tobacco). INTERMED can be helpful to assess biopsychosocial complexity, and psychological testing might be useful in suspected cases of personality disorder or somatic symptom disorder.

Medications. *Serotonin-norepinephrine modulators.* A retrospective study found that most patients with CRPS reported decreased pain from the serotonin norepinephrine reuptake inhibitor (SNRI) venlafaxine, the tricyclic antidepressant (TCA) amitriptyline, and/or the norepinephrine-serotonin antagonist mirtazapine.[12] However, results are interpreted cautiously, as it is unknown whether medications were prescribed alone or in combination, there were no individual drug efficacy assessments, and many patients received concurrent pain medications (e.g., opioids, nonsteroidal anti-inflammatory drugs [NSAIDS], glucocorticoids). It appears

reasonable to offer an SNRI, TCA, or mirtazapine for mood, sleep, anxiety, or pain. Avoid TCAs in patients at risk of suicide due to the potential for lethal overdose.

Anticonvulsants. In the same study, gabapentin and pregabalin were associated with reduced pain, though the above limitations exist regarding individual medication efficacy.[12] In an eight-day placebo-controlled study of 43 patients, carbamazepine delayed the increase in pain following inactivation of a spinal cord stimulator.[24] Carbamazepine might be a good choice in patients with CRPS and affective lability or bipolar disorder.

Selective serotonin reuptake inhibitors (SSRIs). The retrospective forensic study noted that 18 of 50 patients were receiving SSRIs, but did not report the indicated condition or treatment efficacy.[13] In patients with anxiety, depression, or PTSD, SSRIs would be a good treatment choice, given their efficacy and safety profile.

Soporifics. Consider trazodone, melatonin, mirtazapine, or TCAs if insomnia is present. Mirtazapine or TCAs can also treat depression or anxiety, while a TCA could additionally provide pain control. When possible, avoid prescribing benzodiazepines or Z-drugs for patients receiving opioids due to the risk for respiratory suppression, as well as for patients with active substance abuse.

In patients with alcohol use disorder, consider prescribing naltrexone or acamprosate. In patients with opioid use disorder, consider naltrexone or buprenorphine/naloxone. Offer a naloxone rescue kit to patients receiving chronic opioids.

Psychotherapy. Despite absence of high-quality trials, many patients with CRPS receive psychotherapy, often cognitive behavioral therapy (CBT).[13] In a 12-week uncontrolled study, 10 patients with CRPS who received blended group cognitive therapy, relaxation therapy, exposure therapy, and acceptance and commitment therapy (ACT) adjunctively with medication management and physiotherapy showed improved sensorimotor function and decreased trophic symptoms. However, there was no difference in overall pain and quality of life.[25] CBT is indicated for depression, PTSD, anxiety, insomnia, and pain and might be beneficial for patients with CRPS.

In a randomized, controlled trial of 18 patients, those receiving relaxation therapy in conjunction with physical therapy reported additional improvements in skin temperature, as well as pain, range of motion, and edema.[26] Exposure therapy and biofeedback led to resolution of pain in case reports.[8,26]

Patients may find validation and avoid isolation by joining a pain support group.

Motivational interviewing and referral for substance abuse counseling and/or a 12-step program are advised for patients with a substance use disorder.

CONCLUSION

CRPS is a debilitating chronic pain disorder that can negatively impact physical, mental, and social health. Depression, anxiety, trauma, insomnia, and substance use disorders might occur in affected patients. The etiology of CRPS appears to be multifactorial; therefore, effective treatment should be multidisciplinary. The multidisciplinary treatment team should include mental health professionals who can utilize medications and psychotherapy to treat any psychiatric symptoms as well as pain.

DISCLAIMER

The opinions expressed in this article are those of the author and do not necessarily reflect the opinion of the Lexington Veterans Affairs Medical Center, the Department of Veterans Affairs, or the United States Government.

REFERENCES

1. Chang C, McDonnell P, Gershwin ME. Complex regional pain syndrome–autoimmune or functional neurologic syndrome. *J Transl Autoimmun*. 2020;24(4):100080.
2. Sandroni P, Benrud-Larson LM, McClelland RL, Low PA. Complex regional pain syndrome type I: incidence and prevalence in Olmsted county, a population-based study. *Pain*. 2003;103(1–2):199–207.
3. de Mos M, de Bruijn AG, Huygen FJ, et al. The incidence of complex regional pain syndrome: a population-based study. *Pain*. 2007;129(1–2):12–20.
4. Kim H, Lee CH, Kim SH, Kim YD. Epidemiology of complex regional pain syndrome in Korea: an electronic population health data study. *PLoS One*. 2018;13(6):e0198147.
5. Merskey H, Bogduk N. Descriptions of chronic pain syndromes and definitions of pain terms. In: *Classification of Chronic Pain, Second Edition*. Seattle, WA: IASP Press;1994.
6. Harden NR, Bruehl S, Perez RSGM, et al. Validation of proposed diagnostic criteria (the "Budapest criteria") for complex regional pain syndrome. *Pain*. 2010;150(2):268–274.
7. Harden RN, Bruehl S, Stanton-Hicks M, Wilson PR. Proposed new diagnostic criteria for complex regional pain syndrome. *Pain Med*. 2007;8(4):326–331.
8. Shim H, Rose J, Halle S, Shekane P. Complex regional pain syndrome: a narrative review for the practising clinician. *Br J Anaesth*. 2019;123(2):e424–e433.
9. Baronio M, Sadia H, Paolacci S, et al. Molecular aspects of regional pain syndrome. *Pain Res Manag*. 2020;7697214.
10. Kohr D, Tschernatsch M, Schmitz K, et al. Autoantibodies in complex regional pain syndrome bind to a differentiation-dependent neuronal surface autoantigen. *Pain*. 2009;143(3):246–251.
11. de Rooij AM, de Mos M, Sturkenboom MC, et al. Familial occurrence of complex regional pain syndrome. *Eur J Pain*. 2009;13(2):171–177.
12. Brinkers M, Rumpelt P, Lux A, et al. Pain psychiatric disorders in complex regional pain syndrome (CRPS): the role of the consultation-liaison psychiatrist. *Res Manag*. 2018:2894360.
13. Bass C, Yates G. Complex regional pain syndrome type 1 in the medico-legal setting: High rates of somatoform disorders, opiate use and diagnostic uncertainty. *Med Sci Law*. 2018;58(3):147–155.
14. Speck V, Schlereth T, Birklein F, Maihöfner C. Increased prevalence of posttraumatic stress disorder in CRPS. *Eur J Pain*. 2017;21(3):466–473.
15. Urits I, Shen AH, Jones MR, et al. Complex regional pain syndrome, current concepts and treatment options. *Curr Pain Headache Rep.* 2018;22:10.
16. Andersen ML, Araujo P, Frange C, Tufik S. Sleep disturbance and pain: a tale of two common problems. *Chest*. 2018;154(5):1249–1259.
17. Beerthuizen A, van't Spijker A, Huygen FJ, et al. Is there an association between psychological factors and the complex regional pain syndrome type 1 (CRPS1) in adults? A systematic review. *Pain*.

2009;145(1–2):52–59.
18. Ciccone DS, Bandilla EB, Wu W. Psychological dysfunction in patients with reflex sympathetic dystrophy. *Pain*. 1997;71:323–333.
19. de Mos M, Huygen FJPM, Dieleman JP, et al. Medical history and the onset of complex regional pain syndrome (CRPS). *Pain*. 2008;139(2):458–466.
20. Monti DA, Herring CL, Schwartzman RJ, Marchese M. Personality assessment of patients with complex regional pain syndrome type I. *Clin J Pain.* 1998;14:295–302.
21. Park HY, Jang YE, Oh S, Lee PB. Psychological characteristics in patients with chronic complex regional pain syndrome: comparisons with patients with major depressive disorder and other types of chronic pain. *J Pain Res*. 2020;13:389–398.
22. Duong HP, Konzelmann M, Vuistiner P, et al. Psychiatric comorbidity and complex regional pain syndrome through the lens of the biopsychosocial model: a comparative study. *J Pain Res*. 2020;13:3235–3245.
23. Huyse FJ, Lyons JS, Stiefel FC, et al. "INTERMED": a method to assess health service needs. I. Development and reliability. *Gen Hosp Psychiatry*. 1999;21(1):39–48.
24. Harke H, Gretenkort P, Ladleif HU, et al. The response of neuropathic pain and pain in complex regional pain syndrome I to carbamazepine and sustained-release morphine in patients pretreated with spinal cord stimulation: a double-blinded randomized study. *Anesth Analg*. 2001;92(2):488–495.
25. Elomaa M, Hotta J, de C Williams AC, et al. Symptom reduction and improved function in chronic CRPS type 1 after 12-week integrated, interdisciplinary therapy. *Scand J Pain*. 2019;19(2):257–270.
26. Harden RN, Oaklander AL, Burton AW, et al. Complex regional pain syndrome: practical diagnostic and treatment guidelines, 4th edition. *Pain Med.* 2013;14:180–229. ICNS