Complex Regional Pain Syndrome: Contemporary Concepts in Pathophysiology, Diagnosis, Prevention, and Management – An Evidence-Based Narrative Review

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Abstract

Background: Complex Regional Pain Syndrome (CRPS) is a chronic, debilitating pain disorder that typically follows trauma or surgery and is characterized by disproportionate pain, sensory disturbances, vasomotor changes, and motor dysfunction. Despite advances in understanding, CRPS remains diagnostically challenging and therapeutically complex.

Objective: To synthesize current consensus (2018–2024) on the pathophysiology, diagnostic standards, and evidence-based management of CRPS, with a focus on preventive strategies and emerging therapies.

Methods: A narrative review of PubMed, Embase, and Cochrane Library databases (January 2018–June 2024) was performed using the terms Complex Regional Pain Syndrome, Budapest criteria, vitamin C, graded motor imagery, bisphosphonate, ketamine, and neuromodulation. Randomized controlled trials, meta-analyses, and international guidelines were prioritized.

Results: The Budapest clinical diagnostic criteria remain the global gold standard. Early mobilization, vitamin C prophylaxis, and meticulous fracture management reduce incidence after limb trauma. Multimodal treatment combining patient education, intensive physiotherapy, and pharmacologic agents (gabapentin, bisphosphonates, corticosteroids, and NMDA antagonists) provides the best outcomes. Neuromodulation (spinal cord and dorsal root ganglion stimulation) offers sustained pain relief in refractory cases.

Conclusion: CRPS management requires early recognition, prevention in high-risk injuries, and individualized multidisciplinary therapy. Advanced interventional techniques should be reserved for carefully selected patients after structured conservative management.

Keywords: Complex Regional Pain Syndrome, Budapest criteria, vitamin C prophylaxis, Graded motor imagery, Bisphosphonate therapy, Ketamine, Neuromodulation.

Introduction

Complex Regional Pain Syndrome (CRPS) is a chronic neuropathic pain condition characterized by regional pain that is disproportionate to any known trauma and accompanied by autonomic and motor changes. Incidence varies from 5 to 26 per 100,000 person-years, with distal radius and ankle fractures being common triggers.

Historically known as reflex sympathetic dystrophy, CRPS is now classified into CRPS type I (without confirmed nerve lesion) and CRPS type II (with nerve injury).

Despite decades of research, the exact pathophysiology remains incompletely understood, necessitating a multidimensional management strategy.

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Methods

A narrative review was undertaken according to established methodological guidance for evidence syntheses.

- Databases searched: PubMed, Embase, Cochrane Library.
- Time frame: January 2018 to June 2024.
- Keywords: Complex Regional Pain Syndrome, Budapest criteria, vitamin C, graded motor imagery, bisphosphonate,

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ketamine, neuromodulation.

• Selection: Randomized controlled trials, meta-analyses, clinical practice guidelines, and high-quality observational studies.

• Data extraction: Diagnostic criteria, preventive measures, first-line and second-line treatments, and outcome metrics.

Discussion

Pathophysiology

CRPS represents an interaction of:

• Peripheral sensitization with neurogenic inflammation (substance P, CGRP release).

• Central sensitization in dorsal horn and supraspinal centers.

• Autonomic dysregulation with abnormal sympathetic activity.

• Immune involvement, including pro-inflammatory cytokine upregulation.

These processes create a self-perpetuating cycle of pain, vasomotor instability, and trophic changes.

Diagnosis

The Budapest Criteria remain the reference standard:

1. Continuing pain disproportionate to inciting event.
2. ≥3 symptom categories (sensory, vasomotor, sudomotor/edema, motor/trophic).
3. ≥2 sign categories on examination.
4. No alternative diagnosis better explaining the signs/symptoms.

Ancillary investigations (triple-phase bone scan, MRI, quantitative sensory testing) support but do not replace clinical diagnosis.

Prevention

• Vitamin C prophylaxis: 500 mg daily for 45–50 days post-distal radius fracture reduces CRPS incidence.

•Early mobilization and physiotherapy after limb trauma lower risk.

• Optimized fracture fixation and pain control minimize sympathetic overactivity.

Management

Multimodal Rehabilitation

• Physical therapy: active mobilization, mirror therapy, graded motor imagery.

• Occupational therapy: desensitization, functional restoration.

• Psychological support: cognitive behavioral therapy to address kinesiophobia and depression.

Pharmacologic Therapy

• Neuropathic pain agents: gabapentin, pregabalin, tricyclic antidepressants.

• Anti-inflammatory agents: short courses of oral corticosteroids in early disease.

• Bisphosphonates: IV pamidronate or oral alendronate improve pain and function in randomized trials.

• NMDA antagonists: subanesthetic ketamine infusions provide relief in refractory CRPS.

Interventional and Surgical Options

• Sympathetic nerve blocks may provide temporary analgesia and facilitate physiotherapy.

• Neuromodulation: spinal cord stimulation and dorsal root ganglion stimulation show durable pain reduction and improved quality of life in selected patients.

Prognosis

Early diagnosis and intervention are critical. Delay beyond six months is associated with persistent pain and functional decline.

Conclusion

CRPS is a complex neuropathic disorder requiring early recognition, prevention in high-risk injuries, and coordinated multidisciplinary management.

First-line therapy includes patient education, aggressive rehabilitation, and neuropathic pain pharmacotherapy. Bisphosphonates, ketamine, and neuromodulation provide options for refractory disease. Future research should target biomarkers for early detection, predictors of chronicity, and personalized treatment algorithms.

Learning Point of View

• Employ Budapest criteria for timely and accurate diagnosis.

• Initiate vitamin C prophylaxis and early mobilization in high-risk trauma.

• Multidisciplinary rehabilitation remains the cornerstone of therapy.

• Reserve bisphosphonates, ketamine, and neuromodulation for refractory cases.

• Continued research is essential to develop predictive biomarkers and precision medicine approaches.

Declaration of patient consent: The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient has given his consent for his images and other clinical information to be reported in the Journal. The patient understands that his name and initials will not be published, and due efforts will be made to conceal his identity, but anonymity cannot be guaranteed.

Conflict of Interest: NIL; **Source of Support:** NIL

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