Complex Regional Pain Syndrome

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Objectives

• Identify the current diagnostic criteria for CRPS

• Recognize the hallmark of the diagnosis

• Review the current treatments and their evidence
Complex Regional Pain Syndrome Type I

What Is Complex Regional Pain Syndrome (CRPS/RSD)?

- Debilitating chronic pain syndrome characterized by
  - Pain and hypersensitivity
  - Vasomotor skin changes
  - Functional impairment
  - Various degrees of trophic change
- Generally follows musculoskeletal trauma
- Occurs more frequently in young adults and women
- Triggered by trauma (fractures), surgery, inflammation, stroke, crush injury, MI, neoplasms, immobilization, sprains.
- Psychological stressors and poor coping skills can influence natural history and severity of CRPS.
- At least 50,000 new cases of CRPS I occur annually in U.S.

Diagnostic Criteria for CRPS
Budapest Criteria

- Diagnosis of exclusion
- Continuing pain disproportionate to any inciting event
- Patients should report at least one symptom in 3 of the 4 categories and display one sign in 2 or more categories:
  - Sensory: report hypersensitivity or increased sensitivity to a sensory stimulation; evidence of hyperalgesia or allodynia
  - Vasomotor: temperature asymmetry or skin color changes
  - Sudomotor/edema: changes in sweating or edema
  - Motor/trophic: decreased range of motion or weakness, tremor, dystonia or trophic changes (hair, nail, skin changes)
- Designed to retain diagnostic sensitivity of original criteria while doubling specificity (reduce false positives)
- Validity supported; official IASP diagnostic criteria in 2012
Clinical Features of CRPS

- **Systems**: autonomic, sensory, motor changes
- **Symptoms**: stinging, burning pain, aching, shooting, squeezing, throbbing sensations
- **Type I**: lacks specific nerve lesion;
- **Type II** (Causalgia) reflects clear evidence of nerve injury, but symptoms extend beyond the course of the affected peripheral nerve distinguishing it from isolated mononeuropathy
- **Stage I**: early, acute with sensory/vasomotor, autonomic changes
- **Stage II**: increased pain, vasomotor changes, substantial motor/trophic changes
- **Stage III**: diminished pain, sig. increased motor/trophic changes and continued vasomotor changes. No definite sequence occurs in all patients

- More common: transition from warm, red CRPS to cold, bluish common as CRPS progresses from acute to chronic state
- Warm and Cold CRPS: More likely to resolve within 12 months if initially diagnosed with warm CRPS.

Clinical Features of CRPS

- **Hyperesthesia**: increased sensitivity to stimulation
  - **Allodynia**: pain associated with stimulus that normally provokes no pain
  - **Hyperalgesia**: exaggerated painful response to a painful stimulus
- **Limb Disuse**: Animal and human studies report disuse in development of CRPS. Early mobilization important after injury to prevent chronic CRPS.
- **Natural Course**: Many cases probably resolve with limited intervention. Smaller subset of persistent pts seen in tertiary care clinics.

Clinical Features of CRPS

- **Sympathetic Component**: Sympathetic blockade can help distinguish presence
  - SMP = pain maintained by sympathetic efferent system or circulating catecholamines
  - SMP conditions = HZ, CRPS, Phantom pain, neuralgias
  - Sympatho-afferent coupling can trigger pain & play role in severity of syndrome
- **Psychological Component**: Depression common (24% - 49% of pts); higher risk of suicide
  - Anxiety, depression, anger may have greater pain impact due to sympatho-afferent coupling
**Clinical Features of CRPS**

- **Spread Patterns** (not universal; 48% report spreading)
  - Contiguous Spread = enlargement of the affected area (common)
  - Independent spread = location distant and non-contiguous with the initial site (less common)
  - Mirror-image spread = symptoms opposite the area of initial presentation (uncommon)
    - But, mirror image spread is most common according to Van Rijn et al, then contiguous spread

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**CRPS Type I**

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**Evaluation of CRPS**

- **Hallmark of diagnosis**
  - Thorough clinical evaluation of symptoms and signs

- **Laboratory testing**
  - Vascular studies = R/O DVT
  - EMG/NCT = R/O peripheral neuropathy
  - MRI and x-ray = R/O soft tissue, disc, central canal stenosis, neuroforaminal stenosis, bone disease
  - Blood testing = R/O infection, cellulitis, rheumatologic diseases
Evaluation of CRPS, cont’d

- Other Testing – may support clinical diagnosis
- Thermography, Three-phase bone scan, Sudomotor testing, Sympathetic blockade
- Outcome studies fail to support value lab of tests

Pathophysiology – Proposed Model

- Tissue injury elicits cytokines and neuropeptides (TNF-alpha, IL-1b, IL-2, substance P, B cell activation
  - High levels of osteoprotegerin may determine progression to CRPS or if injury resolves normally
- Neural injury may trigger CRPS as well
- Genetic factors may include polymorphisms of Alpha 1a adrenoceptors and the HLA system
- Nerve trauma may cause reduced density of nociceptive fibers causing alteration of sweat glands/hair follicles
- Nociceptive fibers now express adrenergic receptors; SNS and catecholamines can trigger nociceptive firing (sympatho-afferent coupling)
- Decreased SNS outflow after initiating trauma causes vasodilatation

Pathophysiology

- Decreased SNS outflow causes upregulation of local adrenergic receptors leading to vasoconstriction in presence of catecholamines
- Regional blood flow reductions cause local hypoxia leading to trophic changes
- Ongoing nociceptive input produces central sensitization (spinal cord)
- Altered afferent input from affected extremity contributes to reduced somatosensory representation in the brain
  - Impaired tactile sensation (↑ pain intensity & hyperalgesia)
- Result: CRPS reflects a disease of the CNS as well as SNS
  - Evidence of changes in somatosensory systems’ processing tactile, thermal, noxious stimuli

Pathophysiology

• Possible mechanisms involved in complex regional pain syndrome
  • Nerve injury
  • Ischemic reperfusion injury or oxidative stress
  • Central sensitization
  • Peripheral sensitization
  • Altered sympathetic nervous system function or sympatho-afferent coupling
  • Inflammatory and immune related factors
  • Brain changes
  • Genetic factors
  • Psychological factors and disuse

Fig. 1. Speculative model of interacting complex regional pain syndrome mechanisms. CGRP = calcitonin gene-related peptide; IL = interleukin; TNF = tumor necrosis factor.

• Brain Changes
  • Endogenous pain inhibitory pathways impaired (opioid mediated)
  • Reduced representation of affected limb in primary/secondary somatosensory cortices
    • Why? Increase somatosensory representation of unaffected limb
  • Motor changes too – disinhibition of primary motor cortex
  • Structural changes – reduced gray matter in insula and cingulate cortex (affective pain component)
  • Successful treatment can normalize altered somatosensory representation

• Autoantibodies
  • Serum studies of CRPS pts show autoantibodies against autonomic structures (Beta 2 adrenergic; muscarinic type 2 receptors)
  • CRPS may have autoimmune pathology in subset of pts
Onset

- Symptoms should occur within first few weeks of initiating event, based on mechanisms
- Data suggest development during 3 - 4 month window after initiating injury
  - Onset after this period unlikely and hard to explain mechanistically
- Studies suggest more severe pain early after initiating event & longer CRPS-like presentation, more likely to be CRPS versus delayed normal healing

Risk Factors

- Possible links between asthma, migraine, osteoporosis and later development of CRPS
- Significant association between concurrent use of ACE inhibitors and CRPS risk
- Females 3 X more likely affected

Treatment

- Multidisciplinary
  - Physical and Occupational Therapy
  - Medical
  - Psychological
  - Interventional
- General conclusion from recent reviews
  - Little support from high quality RCTs for many treatment approaches
  - Both reviews suggest efficacy for physical and occupational therapy, bisphosphonates, subanesthetic ketamine
  - Agreement that sympathetic blocks probably less effective
Treatment

- **Multimodal Approach:** early, aggressive
  - Goals: Normalize use of affected limb and prevent disuse
    - Incorporate motor therapy and graded motor imagery
- **Modalities**
  - Pharmacotherapy
    - TCAs, Anticonvulsants, Corticosteroids, Opioids, Tramadol, Bisphosphonates, Sympatholytic agents, Calcitonin, Ketamine
  - Sympathetic Nerve Blocks: Stellate Ganglion and Lumbar Sympathetic
  - Neuromodulation
    - Intrathecal Baclofen for Dystonia
  - Behavioral Approaches
  - Surgical Sympathectomy

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Treatment

- **Physical and occupational therapy**
  - Scrubbing, stress loading, desensitization, myofascial release, isometric strengthening
  - Steroids
    - Pulse of oral steroids in acute stage may improve symptoms
    - 30-40 mg prednisolone x 2 weeks and taper
  - Gabapentinoids
    - Gabapentin – mild analgesia, but sign. reduction in sensory deficits
  - Antidepressants
    - Meta analyses support TCAs for non CRPS neuropathic pain
  - Transdermal Lidocaine
    - No RCTs
  - Opioids
    - Only to facilitate functional therapies and daily activities

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Treatment

- **Psychological Treatment**
  - Pain focused CBT typically beneficial for chronic CRPS
  - Sympathetic Blockade
    - Stellate ganglion blocks/lumbar sympathetic blocks may assist in functional therapies for those with sympathetically maintained pain
    - Not curative
  - Spinal Cord Stimulation
    - Beneficial, but efficacy can diminish over time (3-5 years)
  - Ketamine (NMDA antagonist, IL-6 & TNF-alpha): affects central sensitization (hyperalgesia, allodynia) and cytokine release (immunomodulator)
    - Topical ketamine and subanesthetic infusions may hold promise for refractory CRPS; weaker support for anesthetic doses (ketamine coma).
    - Hepatic injury possible with repeat infusions
### Treatment

- **Bisphosphonates**
  - Agents show promise in small RCTs; inhibit osteoclastic bone resorption
  - Rationale: Impaired bone metabolism may occur in CRPS
  - Most benefit if days duration <12 months

- **Antioxidants**
  - Dimethyl sulfoxide – warm CRPS
  - Oral N-acetylcysteine – cold CRPS
  - Significant relief typically for 17-52 weeks

- **Calcitonin**
  - Agents show promise in small RCTs
  - Inhibits osteoclasts and has independent antinociceptive effect
  - Most benefit if days duration >12 months

- **Intrathecal therapies (pain pumps)**
  - Baclofen – benefit in reducing dystonia and pain

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### Rehabilitation

- **Desensitization of the affected region**

- **Mobilization, edema control, and isometric strengthening**

- **Stress loading, isotonic strengthening, range of motion, postural normalization and aerobic conditioning**

- **Vocational and functional rehabilitation**

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### Novel Therapies

- **Mirror Box Therapy**
  - First described for treatment of phantom limb pain
  - Moving unaffected limb in front of mirror causes cortical reorganization of the sensory homunculus
  - Included in functional therapy programs

- **IV Immunoglobulin**
  - Interferes with autoantibodies and down regulates proinflammatory cytokines
  - Small RCT found efficacy

- **Lose dose naltrexone**
  - RCT ongoing; may reduce glial inflammation
Novel Therapies

- **Cannabinoids**
  - Emerging support in peripheral and central neuropathic pain conditions

- **Botulinum Toxin**
  - Reports and observations show improvement in dystonia, pain, allodynia after S/Q or IM injection


Novel Therapies

- **Scrambler Therapy**
  - FDA cleared in 2014 for neuropathic and cancer pain
  - Used in Europe for chemotherapy-induced peripheral neuropathy (CIPN)
  - Studies on CRPS, Failed Back Surgery Syndrome, Postherpetic Neuralgia, CIPN
  - Many patients had dramatic relief without side effects
  - Mechanism – transmits 16 sequences of low frequency electrical stimulation; inhibits pain impulse transmission
  - 30-45 minute sessions
  - Relief for weeks to months


Prevention

- **Primary**
  - Vitamin C (reduces inflammation via antioxidant effect)
    - Meta analysis showed substantial reduction in risk of CRPS after limb fracture or surgery (wrist fractures mainly)
    - 500 mg/day for at least 45 days from injury
    - Recent RCT = VI C associated with increase incidence of CRPS at 8 weeks after fracture
    - Conclusion: Use unclear
  - Minimize tourniquet duration & ischemic reperfusion injury

- **Secondary (prevent relapse)**
  - Postpone surgery until signs are minimal
  - Use regional anesthetic techniques (spinal/bilateral plexus block)
  - Salmon calcitonin of 100 IU daily s.c. perioperatively for 4 weeks