COMPLEX REGIONAL PAIN SYNDROME(CRPS)

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What Is CRPS?

- A disorder usually effects distal limbs
- Characterized by pain, swelling, limited range of motion, vasomotor instability, skin changes, and patchy bone demineralization
- Frequently begins following a fracture, soft tissue injury, or surgery
- The pain that is disproportionate in time or degree to the usual course of any known trauma or other lesion

History

- In 1993, the International Association for Study of pain introduced the CRPS

- To describe all the pain states that previously would have been diagnosed as Reflex Sympathetic Dystrophy or Causalgia-Like Syndromes including, Post traumatic Dystrophy, Causalgia, Sudek Atrophy, Shoulder Hand Syndrome, Reflex Sympathetic Dystrophy.

CRPS

- Complex: dynamic Clinical Presentation
- Regional: non dermatomal distribution
- Pain: Out of Proportion to the inciting event
- Syndrome: a group of symptoms

Subtypes

- Type I (the form also known as Reflex Sympathetic Dystrophy) corresponds to patients with CRPS without evidence of peripheral nerve injury and represents approximately 90 percent of clinical presentations.

- Type II was formerly termed "causalgia" and refers to cases in which peripheral nerve injury is present.

Pathogenesis

- **Inflammation**: Classic and neurogenic inflammation. There are significant increases in inflammatory cytokines (IL-1beta, IL-2, IL-6, and TNF-alpha) in affected tissue as well as in plasma and cerebrospinal fluid. the release of inflammatory mediators and pain-producing peptides by peripheral nerves produce pain.

- **Central sensitization**: increased activity in nociceptive afferents due to peripheral noxious stimuli, tissue damage, or nerve injury leads to increased synaptic transmission at somatosensory neurons in the dorsal horn of the spinal cord

- **Sympathetic nervous system**: the role of sympathetic nervous system in CRPS is unclear; however, autonomic manifestations previously ascribed to sympathetic overactivity could be due to catecholamine hypersensitivity

Epidemiology

- 5 and 26 per 100,000 per year. CRPS is more common in women, with a female-to-male ratio of 2:1 to 4:1 . The incidence appears to be highest in postmenopausal women.

https://journals.lww.com/pain/Abstract/2007/05000/The_incidence_of_complex_regional_pain_syndrome__A.5.aspx

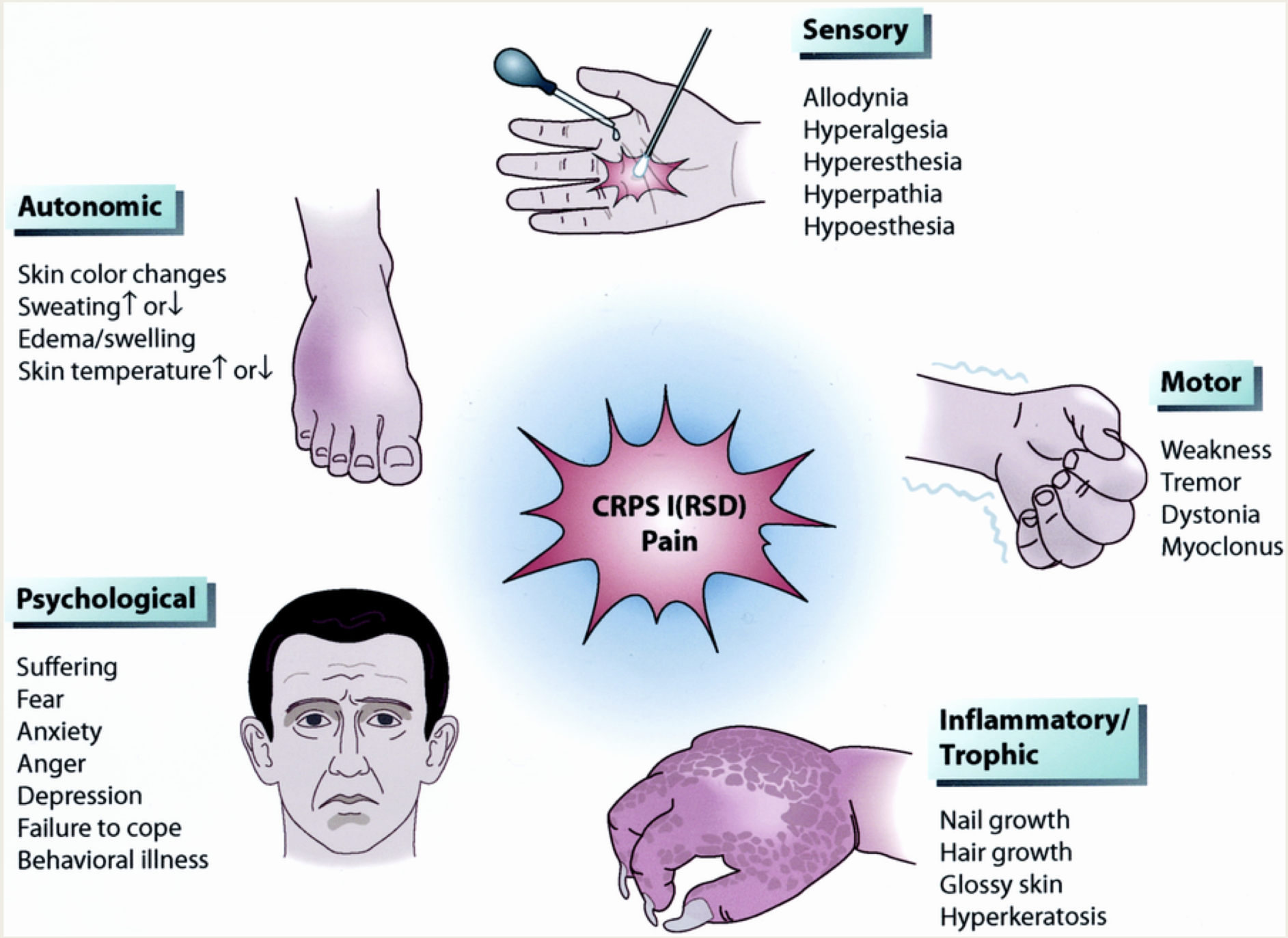
- **Inciting events:** fractures (44 percent), blunt traumatic injuries including sprains (21 percent), surgery (12 percent), no precipitating factor (10 percent), carpal tunnel syndrome (7 percent)
- **genetic factors:** One case-control study reported a significantly increased frequency of HLA-DQ1 among patients affected by CRPS type I. The results of another study suggested that the phenotype of CRPS that progressed to develop multifocal or generalized dystonia was associated with HLA-DR3

https://www.ncbi.nlm.nih.gov/pubmed?term=12749963

Clinical Manifestations

The onset of CRPS generally occurs within four to six weeks of the inciting event

- **Pain:** burning, stinging, or tearing sensation that is felt deep inside the limb in most cases, though it may be superficial in some cases. Pain may be worse at night and exacerbated by limb movement, contact, temperature variation, or stress.
- **Sensory changes:** hyperalgesia, allodynia, or hypesthesia on examination. Sensory disturbances are usually distal in the limb.
- **Motor Impairments:** two-thirds of patients have functional motor impairments related to pain. Impairment is typically manifest by a reduction of complex muscle strength. Some patients develop central motor manifestations such as tremor, myoclonus, dystonic postures, or impaired initiation of movement.
- **Autonomic Symptoms:** differences in skin temperature(half of patients had difference in skin temperature of ≥1 degree Celsius), skin color, sweat, or edema
- **Trophic changes:** affecting the connective tissue (increased hair growth, increased or decreased nail growth, contraction and fibrosis of joints and fascia, and skin atrophy).


Sensory
Allodynia
Hyperalgesia
Hyperesthesia
Hyperpathia
Hypoesthesia
Autonomic
Skin color changes
Sweating↑ or↓
Edema/swelling
Skin temperature↑ or↓
CRPS I(RSD)
Pain
Motor
Weakness
Tremor
Dystonia
Myoclonus
Psychological
Suffering
Fear
Anxiety
Anger
Depression
Failure to cope
Behavioral illness
Inflammatory/
Trophic
Nail growth
Hair growth
Glossy skin
Hyperkeratosis

Clinical Stages of CRPS

- **Stage 1** :after an event or without apparent cause, the patient develops throbbing pain, sensitivity to touch or cold, localized edema, and vasomotor disturbances. The radiograph is usually normal but may show patchy demineralization.
- **Stage 2**: progression of the soft tissue edema, thickening of the skin and articular soft tissues, muscle wasting, and the development of brawny skin. This may last for three to six months.
- **Stage 3**: The most severe, limitation of movement, the shoulder-hand syndrome, contractures of the digits, waxy trophic skin changes, and brittle, ridged nails. Severe demineralization

Diagnosis

- NO gold standard test TO confirm the diagnosis.
- Three phase bone scintigraphy: increased uptake in joints distant from the trauma site.
- Side-by-side radiographs: spotty bone decalcification.
- skin temperature: >1°C difference for the affected versus unaffected side.
- Budapest criteria: Sensitivity 82% and specificity 68%

https://www.jpain.org/article/S1526-5900(18)30028-2/fulltext

The Budapest Criteria

- Continuing pain: disproportionate to any inciting event.
- The patient must report at least one symptom in three of the following four categories:
  - **Sensory:** hyperesthesia, allodynia
  - **Vasomotor:** temperature asymmetry, skin color changes, or skin color asymmetry
  - **Sudomotor/edema:** edema, sweating changes, or sweating asymmetry
  - **Motor/trophic:** decreased range of motion, motor dysfunction (weakness, tremor, dystonia), or trophic changes (hair, nail, skin)

The Budapest Criteria

- The patient must have at least one sign at the time of examination in two of the four following categories:
  - **Sensory:** hyperalgesia (to pinprick), allodynia (to light touch, temperature sensation, deep somatic pressure, or joint movement)
  - **Vasomotor:** temperature asymmetry (>1°C), skin color changes 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 to explains the signs and symptoms

Differential Diagnosis

- Infection of skin, muscle, joint, or bone
- Compartment syndrome
- Peripheral vascular disease
- Deep vein thrombosis
- Peripheral neuropathy
- Rheumatoid arthritis
- Thoracic outlet syndrome
- Raynaud phenomenon

Management

- Patient education: Reflex Sympathetic Dystrophy Syndrome Association (RSDSA), https://rsds.org/
- Physical & occupational therapy
- Psychosocial assessment
- Symptomatic pain management

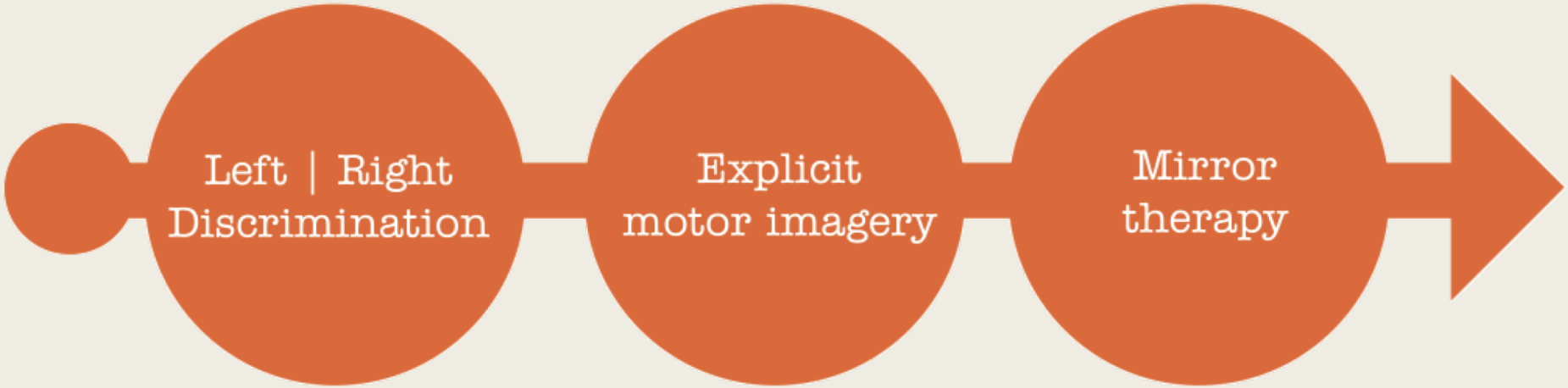
Rehabilitation Techniques

- Graded motor imagery
- Pain-exposure PT and graded exposure in vivo to reduce pain-avoidance behaviors
- Self-administered tactile and thermal desensitization with the aim of normalizing touch perception
- Mirror visual feedback and immersive virtual reality

Rehabilitation Techniques

- Functional movement techniques to improve motor control and awareness of affected limb position
- Principles of stress loading
- Conflict allodynia re-education to reduce fear of physical contact with others in community settings
- the strongest evidence is for graded motor imagery, which led to significant reductions in pain and swelling in patients with CRPS (https://n.neurology.org/content/67/12/2129)

Graded Motor Imagery



Recognise App: https://www.noigroup.com/product/recogniseapp/
Orientate App: https://apps.apple.com/us/app/orientate-pain-management/id479540062

https://youtu.be/fWYUJscRBRw

Consider Referral to Psychologist

- CRPS of more than two months duration at presentation
- Insufficient response to treatment
- Suspected comorbid psychologic or psychiatric disorder

Goals of Pharmacotherapy

- The goal is to use analgesics to reduce pain so that patients can tolerate PT.
- Both pharmacologic and interventional procedures used for pain control.
- Begin with those that are relatively safe and progress to more risky Interventions.
- Pharmacologic therapy should be individualized.

Pharmacotherapy

- **NSAID**
- **Adjuvant medications for neuropathic pain**
  - *patients should understand that although analgesia may occur in days to weeks.*
  - *It is important for patients to know that many of the unpleasant side effects, such as dry mouth, mental clouding, and others, may diminish in days to week**s.***
- **Bisphosphonate**:
  - *In patients with CRPS and evidence of abnormal uptake on bone scan.*
- **Topical & Transdermal Compounds**
- **Other Less Favourable Agents**

NSAIDs

- A typical initial regimen is Ibuprofen 400 to 800 mg three times a day or Naproxen 250 to 500 mg twice daily.
- NSAIDs are generally combined with any of the other agents, so that NSAIDs can be tapered or eliminated over time.
- For patients who cannot tolerate nonselective NSAIDs, a selective cyclooxygenase 2 (COX-2) inhibitor is an alternative option, although direct data in CRPS are lacking.

Anticonvulsants

Potential for **misuse** and **abuse** of these drugs.

- **Gabapentin**: 100 mg at bedtime for older adults and 300 mg at bedtime for most other patients with gradual increase to 2400 mg for older adults and 3600 mg in other patient.
- **Pregabalin:** Initial: 25 to 150 mg/day once daily or in 2 divided doses; may increase in increments of 25 to 150 mg/day at intervals ≥1 week based on response and tolerability up to a usual dose of 300 to 600 mg/day in 2 divided doses
  - *In one placebo-controlled randomized trial of 58 patients with CRPS, gabapentin (maximum 1800 mg daily) produced no significant improvement in pain) https://www.ncbi.nlm.nih.gov/pmc/articles/PMC523854/*
  - *The FDA is warning that serious, life-threatening, and fatal respiratory depression may occur in patients using gabapentinoids (pregabalin, gabapentin), the risk may be increased with the concomitant use of opioids and other central nervous system (CNS) depressants*

Antidepressants

- **Tricyclic antidepressants:** Amitriptyline or Nortriptyline may be started at 10 mg at bedtime and slowly titrated up to an effective analgesic dose 75 mg/day.
- **Dual Uptake Inhibitors:** Serotonin and norepinephrine reuptake inhibitors have demonstrated benefit.
  - Duloxetine Initial: 60 mg once daily; lower initial doses may be considered in patients when tolerability is a concern; maximum dose: 60 mg/day; doses up to 120 mg/day were studied in clinical trials but did not confer any additional benefit.
  - venlafaxine Initial: 37.5 - 75 mg once daily; increase by 75 mg each week to a maximum dosage of 225 mg once daily based on tolerance and effect

Topical Compounds

- A compound analgesic cream: consisting of ketamine 10%, pentoxifylline 6%, clonidine 0.2%, and dimethyl sulfoxide 6% to 10% for CRPS pre-existing for less than 1 year .

https://rsds.org/wp-content/uploads/2016/08/CACandCRPS.pdf

- Other compounds
  - **NSAIDs**: ketoprofen (5-10%), indomethacin (2-4%),piroxicam (2%)
  - diclofenac (5-10%)
  - **Muscle Relaxants:** magnesium (4-10%), baclofen (2-4%) cyclobenzaprine(2-4%)
  - **Anaesthetics:** lidocaine (2-10%), benzocaine (5-20%), tetracaine (3-6%), bupivacaine (0.5-8%), ketamine (3-10%)
  - **Other**: gabapentin (6-10%), amitriptyline (2-5%), diphenhydramine (1-3%), naltrexone (0.5-4.5%),nifedipine (2-10%), clonidine (0.1-0.3%)

Bisphosphonates

- A course of bisphosphonate therapy used for pain reduction in patients with early CRPS who have abnormal uptake on bone scan, The mechanism of analgesic effect in CRPS is uncertain but is Proposed mechanisms include decreased proton concentration in the bone microenvironment, altering pain signal transduction via acid-sensitive ion channels, and decreased production of tumor necrosis factor and other proinflammatory mediators.
- Oral Alendronate at a dose of 40 mg daily for eight weeks

Other Less Favourable Agents

- **Glucocorticoids:** prednisone 30 to 80 mg/day) may be effective for early CRPS, but there is only low-quality evidence from small randomized trials
- **Ketamine:** when Nothing Seems to Help. It is limited by uncertain dosing strategies, low-quality studies demonstrating limited benefit, and poor tolerance due to adverse effects.
  - ***Oral Ketamine: S****tarting with 100 mg in divided doses, titration done every 2 days to final dose of 140-500 mg/day.*
  - ***Intravenous Ketamine:*** *3-7 MG/KG/HR*
- **Low Dose Naltrexone:** due to its ability to increase production of endorphins. Some patients have found success taking LDN for complex regional pain syndrome with decreased pain and improvement in dystonia.
- **Calcitonin**: considering weak evidence for efficacy in CRPS yet low risk associated with its use, calcitonin is an option in combination with PT for patients who have mild or moderate symptoms despite the use of other agents, 100-300international units daily dose.

https://journals.lww.com/pain/Abstract/1992/02000/The_effect_of_adding_calcitonin_to_physical.11.aspx

Take Home Message

- ✓ CRPS is a clinical diagnosis
- ✓ CRPS has no certain cause
- ✓ You should intervene as early as possible
- ✓ Rehabilitation is the cornerstone of treatment
- ✓ CRPS requires a multidisciplinary approach

Any Questions?