Complex Regional Pain Syndrome (CRPS)

Justin Hata, MD
UC Irvine Healthcare
Assistant Clinical Professor
Department of Anesthesiology & Perioperative Care
Department of Physical Medicine & Rehabilitation
Chief, Pain Medicine Division
Director, UCI Center for Pain Management
Co-Director, UCI Comprehensive Spine Program

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Justin Hata, MD
Assistant Clinical Professor, UC Irvine Healthcare

“I have nothing to disclose.”
“I will not discuss off-label use and/or investigational use in my presentation.”

Objectives
1. Define CRPS
2. Discuss work-up
3. Explore treatment options, including medications
4. Explore current concepts
Definition

International Association for the Study of Pain (IASP):

- A variety of painful conditions following injury which appears regionally having a distal predominance of abnormal findings, exceeding in both magnitude and duration the expected clinical course of the inciting event and often resulting in significant impairment of motor function, and showing variable progression over time.

History

- 1600’s: Ambrose Pare described persistent pain & contractures after bloodletting procedure for King Charles IX
- 1700’s: Percivall Pott reports burning pain and atrophy in injured limbs
- 1800’s: Claude Bernard mentioned a syndrome of pain associated with the sympathetic nervous system

Silas Weir-Mitchell

- 1864: “Causalgia” in Civil War soldiers with limb injuries
  - “…the most terrible of all tortures which a nerve wound may inflict…its favorite site is the foot or hand…Its intensity varies from the most trivial burning to a state of torture…The part itself is not alone subject to an intense burning sensation, but becomes exquisitely hyperesthetic, so that a touch or tap of the finger increases the pain.”
Sudeck’s Atrophy
- Early 1900’s: Paul HM Sudeck (Sudeck’s Atrophy, Sudeck’s Dystrophy)

Reflex Sympathetic Dystrophy (RSD)
- 1946: James Evans described “RSD”

Sympathetically Maintained Pain (SMP)
- 1986
- William J. Roberts
- Introduced term “SMP”
- Based on observation that blocking sympathetic nervous system = improvement/regression of symptoms
SMP versus SIP

- Pain relieved by blockade of the efferent sympathetic nervous system
  - “RSD” previously used based on observation that sympatholytic procedures relieved pain in many patients
  - Not all patients with CRPS have SMP
  - Not all SMP is CRPS
- CRPS patient may have sympathetically independent pain (SIP) introduced by Campbell and Meyer in 1992

Mechanism of SMP

- Normal response to injury is activation of sympathetic reflex arc
- SMP involves prolonged continuation of the sympathetic reflex arc
  - Hyperdynamic state of vasoconstriction, tissue ischemia, and pain
  - Increased activity and β-adrenergic receptor sensitivity of nociceptive neurons
  - Nociceptors now activated by norepinephrine release by sympathetic fibers

Mechanism of SMP
1993 Special Consensus Workshop (IASP) in Orlando, FL
- “Complex Regional Pain Syndrome”
- Descriptive and general term
- Not meant to imply etiology/pathology
- Subtypes
  - Type I: RSD (without “nerve damage”)
  - Type II: Causalgia (with “nerve damage”)
  - Sympathetically maintained pain (SMP)
  - Sympathetically independent pain (SIP)

1993 IASP diagnostic criteria for CRPS
1. The presence of an initiating noxious event, or a cause of immobilization
2. Continuing pain, allodynia, or hyperalgesia disproportionate to any known inciting event
3. Evidence at some time of edema, changes in skin blood flow, or abnormal sudomotor activity in the region of pain
4. Diagnosis is excluded by the existence of other conditions that would otherwise account for the degree of pain and dysfunction

2003 International Consensus CRPS Workshop in Budapest
- “Closed” (invitation only) workshop
- 35 attendees, 7 countries
- Proposed modified clinical diagnostic criteria for CRPS (IASP)
“Budapest” criteria

Current Terminology

- CRPS Type I
  - aka Reflex Sympathetic Dystrophy (RSD)
  - Without major nerve damage

- CRPS Type II
  - aka Causalgia
  - With major nerve damage

Sensory Disturbances
Autonomic Disturbances

- Sympathetic deficit
  - Warmth
  - Loss of vasoconstrictor reflexes
- Sympathetic over-activity
  - Sweating
  - Coldness
- Cold pattern commonly in CRPS patients with the longest duration of pain
  - Warm, dry limb of CRPS can evolve into a cool moist limb as the condition progresses

Motor Disorders (MDs)

- Loss of voluntary control
- Bradykinesia
- Dystonia
- Myoclonus
- Tremor
- May occur early in the disease course
- Prevalence of MDs increases as the disease duration lengthens

CRPS Clinical Stages

Stage 1: Burning, throbbing pain; localized edema; skin color changes; allodynia
Stage 2: Soft tissue edema, skin thickening, muscle atrophy
Stage 3: Limited ROM, contractures, waxy skin changes, bone radiography shows severe demineralization
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Stages of CRPS

<table>
<thead>
<tr>
<th></th>
<th>Acute</th>
<th>Dystrophic</th>
<th>Atrophic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain</td>
<td>Localized, severe, burning</td>
<td>Diffuse, throbbing</td>
<td>Less severe, may involve other extremities</td>
</tr>
<tr>
<td>Extremity</td>
<td>Warm</td>
<td>Cold, cyanotic, edematous, muscle wasting</td>
<td>Severe muscle atrophy, contractures</td>
</tr>
<tr>
<td>Skin</td>
<td>Dry and red</td>
<td>Sweaty</td>
<td>Glossy and atrophic, waxy</td>
</tr>
<tr>
<td>X-ray</td>
<td>Normal</td>
<td>Osteoporosis</td>
<td>Severe osteoporosis; ankylosis of joint</td>
</tr>
<tr>
<td>Duration</td>
<td>1-3 months</td>
<td>3-6 months</td>
<td>Indefinite</td>
</tr>
</tbody>
</table>

Diagnostic Tests

- Bone scintigraphy (stage 1 or 2)
- Plain radiographs (stage 2 or 3)
- fMRI
- Quantitative Sensory Testing (QST)
- Autonomic testing (QSART)
  - Sweat output
  - Skin temp
- Diagnostic Injections for SMP
  - Sympathetic Block
  - Regional IV Blockade
  - Phentolamine Infusion Test

Bone Scintigraphy

- Bone scintigraphy – increased blood flow, pooling, and periarticular uptake (subacute stage up to 1 year)
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X-Ray

X-ray – patchy demineralization (chronic stage)

fMRI

CRPS patients
- Marked differences of insular and Posterior Cingulate Cortex (PCC) activation
- Activation of the anterior insula, PCC, and caudate
- Compared with controls, CRPS patients had stronger activation of the PCC during painful stimulation of the symptomatic hand

Quantitative Sensory Testing

Quantitative Sensory Testing (QST)
- Non-invasive psychophysical method used to assess severity of nerve damage
- Cold detection threshold
- Vibration detection threshold
- CRPS patients:
  - Increase in warm perception thresholds
  - Decrease of cold pain thresholds
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Autonomic Testing

- Infrared Thermography
- Laser Doppler Flowmetry
- Quantitative Sudomotor Axon Reflex Test (QSART)

Infrared Thermography

Non-invasive imaging technique measuring temperature distribution in tissues

Laser Doppler Flowmetry

Non-invasive imaging technique to assess skin blood flow
Quantitative Sudomotor Axon Reflex Test (QSART)

- Autonomic function test of small nerve fibers linked to sweat glands
- Measures
  - Resting skin temperature
  - Resting sweat output
  - Stimulated sweat output

Treatment
**Physical/Occupational Therapy**

- Both PT & OT have positive effect

**Acute Stage**
- Immobilization
- Careful contralateral PT

**Dystrophic Stage**
- Passive PT with active isometric exercises
- Isotonic training
- Sensory desensitization program

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**2010 European EBM Guidelines for CRPS Type I**

- Multidisciplinary task force
- Literature review of treatment effects for CRPS I
- Studies published between 1980 – 2005
- Conclusions:
  - For pain treatment: WHO analgesic ladder is advised
  - For neuropathic pain: anticonvulsants and TCAs
  - For inflammatory symptoms: free radical scavengers (DMSO or N-acetylcysteine)
  - To promote blood flow: vasodilatory medication and sympathetic blockade show insufficient effect
  - PT/OT advised to decrease functional limitations
  - Vitamin C for primary prevention after wrist fx
  - **Further research needed!**

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**Medications: 2010 European EBM Guidelines**

- No evidence or insufficient evidence for beneficial effect
  - Tylenol
  - NSAIDs
  - Opioids
  - Local anesthetics
  - Antidepressants
  - Capsaicin
  - Oral muscle relaxants
  - Botulinum toxin
  - Intrathecal baclofen administration
Medications: 2010 European EBM Guidelines

- Limited evidence of beneficial effect
  - Anticonvulsants: Limited evidence beneficial
  - Ketamine: Limited evidence beneficial
  - Free radical scavengers: Limited evidence
    - 50% DMSO cream effective for warm CRPS I
    - N-acetylcysteine for cold CRPS I
  - Corticosteroids: Limited evidence beneficial
  - Bisphosphonates: Beneficial, unknown optimal dosing, frequency, duration of treatment
  - Calcium-channel blockers: Limited evidence beneficial
  - Calcitonin: Conflicting evidence

Sample Dosages

- Gabapentin: 300 mg 3x/day, titrate up to 800 mg 3x/day
- Dimethylsulphoxide (DMSO): 50% cream, apply 5x/day to the affected extremity
- N-acetylcysteine (NAC): 600 mg effervescent tablets 3x/day
- Oral prednisone: 10 mg 3x/day until clinical remission, max 12 weeks
- Nifedipine: 20 mg 1x/day (acute phase)

Primary prevention medications (Pre-operative)

- Primary prevention medications
  - Vitamin C
    - 500 mg/day x 50 days (7% vs 22% in casted wrist fx)
    - 1000 mg/day x 45 days (2% vs 10% in wrist fx treated with surgery)
  - Guanethidine – Not indicated
  - Calcitonin – Not indicated
- Secondary prevention medications
  - Regional anesthesia with lidocaine + clonidine
Interventions

- **Sympathetic blockade**: Not useful for Tx
- **Sympathectomy** – Indications that may improve pain: surgical, chemical, or radiofrequency
- **IV Regional Block** – No indication w/bretylium, guanethidine, local anesthetic, clonidine, ketoralac
  - Possible improvement w/ketanserine or Infliximab
- **Neuromodulation** – Indication for pain reduction and improved QOL: spinal cord stimulators (SCS)

Psychotherapy

- Biofeedback
- Stress Management
- Relaxation Training
- Family Therapy

Movement Disturbances Treatment

- No RCT of PT, OT, or oral pharmacotherapy in treatment of MDs in CRPS
- Splints or plaster casts are often ineffective
  - May even worsen dystonic postures of CRPS
- BZD and high doses of baclofen may be beneficial in the treatment of dystonia and spasms
- No controlled studies for use of botulinum toxin in dystonia
- Intrathecal baclofen: 1 study, small cohort, improved dystonia
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Treatment Goals

- Multidisciplinary approach
  - Physical/Occupational therapy
  - Medications
  - Interventions
  - Cognitive behavioral techniques
  - Preventative measures
- Early detection and treatment

Current Applications

- Increased risk of CRPS in modern day warfare
  - Improvements in armor, military medicine result in less deaths, but more severe injuries
  - Military is focusing on prevention in combat zone
- Regional techniques (epidural, CPNB) for analgesia prior to surgery
  - Decrease sensitization and prevention of prolonged sympathetic activation
- Objectification of diagnostic criteria

Objectification of CRPS Diagnostic Criteria

- R. Norman Harden (2010)
  - “…scientifically problematic to add more data elements that are also fully subjective (patient report) or weakly objective (practitioner observation)…”
  - “Hypothetically, objectifying and quantifying as many criteria as possible will enhance diagnostic accuracy and research efficiency…”
Sensory Factors

- Quantify pain by visual analog scale (VAS), if practical.
- Document qualities of pain using the McGill short-form.
- Quantify temperature allodynia by a standard Peltier-type device.
- Quantify mechanical allodynia using von Frey testing.
- Measure deep mechanical sensitivity by algometer, over muscle and joint.
- Functional imaging provides the best data: a fully objective correlate with evoked pain (and hyperalgesia)
- Quantitative Sensory Testing

Vasomotor Factors

- Laser Doppler: direct, fully objective measure of vasomotor tone
- Limb temperature: indirect, yet objective measure of cutaneous and subcutaneous blood flow
- Methods in order of objectivity and quantification:
  - Infrared telemthermography, thermistors, thermometers, and temperature tape
  - “Space suits”: manipulate and measure vasomotor tone experimentally

Sudomotor/Edema Factors

- Can be objectively measured
  - Quantitative sudomotor axon response testing
- Indirectly measured (and patterned) using
  - Bioimpedance (skin conductance testing)
  - Skin potential fluctuations (sympathetic skin response testing)
- Edema can be quantitated using volumetry
## Motor Factors
- Subjectively quantitate weakness by scores
- Features of certain motor signs can be measured, such as bradykinesia and general activity (e.g., accelerometer)
- Currently no reliable scores or metrics for myoclonus, athetosis, dystonia, or contracture
- Skin, nail, or hair trophic changes use subjective measures
- Range of motion: Goniometer
- Bone density (Sudeck’s atrophy) can be measured
- Small nerve density can be quantitated

## Take Home Points
- CRPS I (aka RSD) = NO nerve injury
- CRPS II (aka causalgia) = nerve injury
- Non-dermatomal pain out of proportion to inciting event
- Objectification of autonomic, motor, trophic, or sensory changes
- SMP may or may not be present
- Multidisciplinary treatment with medications, PT, interventions, psychotherapy

## References