Complex Regional Pain Syndrome

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Learning Objectives

- Historical Perspective
- Diagnostic Criteria
- Risk Factors
- Pain Management
Clinical Features

Pain syndrome resulting in sensitivity, swelling, and skin changes to an affective limb

CRPS I (RSD): without nerve injury

CRPS II (Causalgia): known nerve injury
Historical Perspective

1634
French Surgeon Ambrose Pare:
King Charles IX suffered from pain & contractures of the arm after blood letting procedure

1864
Silas Weir Mitchell
“Causalgia”

“Gunshots Wounds and Other Injuries”

1900
Paul Sudeck
Therapy resistant pain “Sudeck’s Atrophy”

1916
Rene Leriche
“Excessive sympathetic activity”

1967
Neurosurgeon Norman Shealy
implants Spinal Cord Stimulator

1994
Complex Regional Pain Syndrome

2003
Budapest Criteria

1994
International Association for the Study of Pain (IASP)

Working together for pain relief
**Budapest Criteria for CRPS**

All of the following statements must be met:
- The patient has continuing pain that is disproportionate to any inciting event
- At least 1 sign in 2 or more of the categories below
- Report at least 1 symptom in 3 or more of the categories below
- No other diagnosis can better explain the signs and symptoms

<table>
<thead>
<tr>
<th>No.</th>
<th>Category</th>
<th>Sign/Symptom</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Sensory</td>
<td>Allodynia (pain to light touch and/or temp. Sensation and/or deep somatic pressure and/or joint movement) and/or hyperalgesia (to pinprick)</td>
</tr>
<tr>
<td>2</td>
<td>Vasomotor</td>
<td>Temperature asymmetry and/or skin color changes and/or skin color asymmetry</td>
</tr>
<tr>
<td>3</td>
<td>Sudomotor/edema</td>
<td>Edema and/or sweating changes and/or sweating asymmetry</td>
</tr>
<tr>
<td>4</td>
<td>Motor/trophic</td>
<td>Decreased range of motion and/or motor dysfunction (weakness, tremor, dystonia) and/or trophic changes hair/nail/skin</td>
</tr>
</tbody>
</table>
CRPS Today

- 5.46 new cases per 100,000 (Sandroni et al. 2003)
- 25.2 new cases per 100,000 (de Mos et al. 2008)
- Often after surgical procedure
Pathophysiology
Genetic Pattern of CRPS Remains Elusive

Human Leukocyte Antigen (HLA-DQ8) -independently associated with CRPS-1 in 131 patients

OR = 1.65 [95% CI 1.12–2.42], \( P = .014 \)

Trauma-RElated Neuronal Dysfunction (TREND) consortium.

van Rooijen (et al 2012). The Journal of Pain
Inheritance Pattern familial CRPS unclear

Familial occurrence of complex regional pain syndrome

Annetje M. de Rooij*, Marissa de Mosb, Miriam C.J.M. Sturkenboomb, Johan Marinusb, Arn M.J.M. van den Maagdenbergc, Jacobus J. van Hiltend

*Department of Neurology, Leiden University Medical Center, Leiden, The Netherlands
bDepartments of Medical Informatics and Epidemiology and Biostatistics, Erasmus Medical Center, Rotterdam, The Netherlands
cDepartment of Human Genetics, Leiden University Medical Center, Leiden, The Netherlands

31 families with two more family members with CRPS (84 patients total)

Familial when compared with sporadic CRPS:

Affected younger patients: ~34 yrs vs 51yrs
More likely to have multiple extremities affected
More likely to have dystonia

Unclear Inheritance Pattern
Genetic Pattern of CRPS Remains Elusive

Reflex sympathetic dystrophy: complex regional pain syndrome type I in children with mitochondrial disease and maternal inheritance

T Higashimoto,1,2,3 E E Baldwin,1,4 J I Gold,5,6 R G Boles1,2

Mitochondrial d/o:
8/8 children with CRPS-1 also with mitochondrial disease
Risk Factors

- High Pain Scores
- Immobilization
- Fibromyalgia

4:1
Roh et al 2014

Post-Menopausal
Vitamin C may prevent the development of CRPS

3 RCTs (Total of 875) patients with wrist fracture

Treatment was non-operative in 758/890 (85.1%) fractures and operative in 132 (14.9%) fractures.

Vitamin C supplementation was started on the day of the injury and continued for 50 days.

In the group given 500 mg of vitamin C daily, the risk ratio for CRPS-I was 0.54 (95%CI, 0.33–0.91; P = 0.02).
CRPS Management

- Physical Therapy
- Sympathetic Blockade
- Neuromodulation
- IV infusions
CRPS Management

- Physical Therapy
- Sympathetic Blockade
- IV infusions
- Neuromodulation
Physical Therapy

N = 135
Patients with CRPS I

PT vs OT vs Control

**VAS:** PT and OT resulted improved VAS pain scores especially in the first 6 months of therapy.

**McGill Pain Questionnaire:** PT was superior to OT and Control at 1 year. ) P < 0.05

**Active Range of Motion:** PT and OT showed statistically significant improvement up to 6 months but no different with control at 1 year.
Physiotherapy for pain and disability in adults with complex regional pain syndrome (CRPS) types I and II

Keith M Smurra1, Benedict M Watt2, Neil E O'Connell3

1Physiotherapy Department, St Vincents University Hospital, Dublin, Ireland. 2School of Physiotherapy, The University of Newcastle, Australia. 3Department of Clinical Sciences/Health Economics Research Group, Institute of Environment, Health and Society, Brunel University, Uxbridge, UK.

18 Studies BUT 15 of these studies high risk for bias
Mirror Therapy
2 RCTs (N = 48)
moderate benefit (VAS), sustained for 6 months

Very low quality of evidence
Virtual body swapping

RCT (N=10 patients)

Very low quality of evidence

Jeon et al 2014

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Sympathetic Blockade

Findings

- LASB vs placebo/sham: No statistically significant and clinically important differences in pain scores at one-year
- LASB w/steroid vs placebo: Statistically significant and clinically important difference in pain at one year
- 8 small studies mostly found no significant difference between LASB vs “other” treatments

12 RCTs  N = 461
Sympathetic Blockade

Findings

- LASB vs placebo/sham: No statistically significant and clinically important differences in pain scores at one-year.
- LASB w/steroid vs placebo: Statistically significant and clinically important difference in pain at one year.
- 8 small studies mostly found no significant difference between LASB vs “other” treatments.

...the limited data available do not suggest that LASB is effective for reducing pain in CRPS.

12 RCTs N = 461
CRPS Management

- IV infusions
- Physical Therapy
- Sympathetic Blockade
- Neuromodulation
Ketamine

Anesthetic vs Subanesthetic dosing

- Case reports of complete pain relief w/anesthetic dosing has been described in the literature

- 3mg/kg/hr usually VS 0.35mg/kg/hr (~max 25mg/hr)

- Anesthetic dosing requires ICU monitoring, intubation, and sedation with benzodiazepine.

- Sympathetic may activation requiring treatment
Ketamine "Coma" induces fMRI changes in patients with CRPS

3mg/kg/hr to 7mg/kg/hr

fMRI:
Anterior Cingulate Cortex lost in CRPS patients but present when pain treated
Ketamine “Coma” induces fMRI changes in patients with CRPS

- Clinically: Pain improved
- Post-ketamine infusion
- Cold Stimulus: Decrease in response
- Temporal lobe & hippocampus activation
Subanesthetic Dose Ketamine shows some efficacy in treating CRPS

63 patients with chronic pain.

22 patients with CRPS

0.1-0.3mg/kg/hr ketamine (4-8 hours/day x 3 consecutive days)

20% reduction in morphine use
MOA of Ketamine

MOA: NMDA-R vs mTOR vs both?

NMDAR inhibition-independent antidepressant actions of ketamine metabolites


Affiliations | Contributions | Corresponding author
--- | --- | ---
Nature 533, 481–486 (26 May 2016) | doi:10.1038/nature17998
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Ketamine

- Ketamine $\rightarrow$ norketamine (80%) $\rightarrow$ hydroxynorketamine (HNK) (15%)

- HNK: Unlike norketamine, NOT an anesthetic or psychostimulant, AND very weak affinity for NMDA receptor

- In animal studies, preventing ketamine conversion to HNK prevented anti-depressants effects, NO dissociative or euphoric effects

- HNK: increase of function of mammalian target of rapamycin (mTOR)

HNK in the treatment of pain in CRPS?
Bisphosphonates

Inhibit bone resorption by decreasing osteoclastic activity.

Unclear MOA in CRPS

5 RCTs

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<th>Intervention vs Placebo</th>
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<td>Alendronate 7.5mg IV q day x 3 days</td>
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<td>Clodronate 300mg IV qday x 10 days</td>
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<tr>
<td>Robinson et al (2004)</td>
<td>Pamidronate 60mg IV qday x 1 dose</td>
</tr>
<tr>
<td>Manicourt et al (2004)</td>
<td>Alendronate 40mg PO qday x 56 days</td>
</tr>
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<td>Varenna et al (2013)</td>
<td>Neridronate 100mg IV x 4 doses over 10 days</td>
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Findings

Improved pain scores
Disease severity score
Physical function/ROM
Bisphosphonates

Inhibit bone resorption by decreasing osteoclastic activity.

Unclear MOA in CRPS

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Findings

Improved pain scores
Disease severity score
Physical function/ROM

Side effects: Transient hypocalcemia w/o symptoms, transient flu-like symptoms, transient fever, and nausea.
Bisphosphonates

A closer look at Varenna et al. 2013

Findings
- Improved pain scores
- Disease severity score
- Physical function/ROM

After 50 days
CRPS Management

- IV infusions
- Physical Therapy
- Sympathetic Blockade
- Neuromodulation
Based on literature-contingent considerations of safety, efficacy, cost efficacy, and cost neutrality, we conclude that SCS should not be considered a therapy of last resort for CRPS but rather should be applied earlier (e.g., three months) as soon as more conservative therapies have failed.

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<th>Appropriateness</th>
<th>Fiscal neutrality</th>
<th>Efficacy</th>
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<td>-Infection 100/2972 cases 3.4%), -Hematoma 8/2972 cases; 0.3%), -Paralysis (1/2972 patients or 0.03%), -CSF leak (8/2972 patients or 0.3%), -skin erosion (0.03%)</td>
<td>Importance of psychological evaluation. Without evaluation: 33% success rate With Evaluation: 70% success rate</td>
<td>Over 5-year Period SCS: $29,123 VS Conventional Therapy: $38,029</td>
<td>2009 Taylor et al: Systematic review (1 RCT, 25 case series. 1 cost-effective study) CRPS type I (Level A evidence) CRPS type II (Level D evidence)</td>
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More DRG patients had >50% pain reduction than SCS

Better mood scores in DRG at 12 months
# Symptom Based Treatment Strategy for CRPS as Used in Eramus Medical Center, Netherlands

<table>
<thead>
<tr>
<th>Step</th>
<th>Warmth</th>
<th>Coldness</th>
<th>Neuropathic Pain</th>
<th>Dystonia</th>
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<tbody>
<tr>
<td>Step 1</td>
<td>Vitamin C: 1g daily PT</td>
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<tr>
<td></td>
<td></td>
<td>Verapamil SR 240mg qdaily</td>
<td>Pregabalin: 75mg qday up to 300mg po qday</td>
<td>Magnesium Sulfate: 200mg TID</td>
</tr>
<tr>
<td>Step 2</td>
<td>Capsaicin Cream x 2 weeks</td>
<td>Add Isosorbidedinitrate cream 1, topical 4 times a day</td>
<td>Add amitriptyline: 25mg increase to Max 75mg/daily dose Or Add duloxetine 30mg daily, increase to 30mg BID</td>
<td>Add clonazepam: 2mg a day, increase to max of 4mg BID</td>
</tr>
<tr>
<td>Step 3</td>
<td>Bisphosphonates Pandromic acid 60mg IV qmonthly for 3 months</td>
<td>Sympathetic Block</td>
<td>Transcutaneous Electric Neuronal Stimulation (TENS)</td>
<td>Add Baclofen</td>
</tr>
<tr>
<td>Step 4</td>
<td>Infliximab 1-3 times within a 1 month period: 3-5mg/kg IV</td>
<td></td>
<td>Opioids</td>
<td>Add Tizanidine</td>
</tr>
<tr>
<td>Step 5</td>
<td>Spinal Cord Stimulation</td>
<td></td>
<td>Intrathecal Baclofen</td>
<td></td>
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Adapted from *Pain in Women: Complex Regional Pain Syndrome* de Mos & Huygen
**Future Directions**

- Over 100 clinical trials
- Vitamin C
- IV Ig infusion
- Low dose naltrexone
- Transcranial Magnetic Stimulation
Thank you for your attention!

Columbia University Medical Center