Complex Regional Pain Syndromes I/II
Reflex Sympathetic Dystrophy/Causalgia

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Reflex Sympathetic Dystrophy

- **Michell, 1864** – Gun shot Wounds
- **Leriche, 1916** – Vascular insufficiency
- **Evans, 1946** – Sympathetic Hyperactivity, term RSD
- **Bonica, 1990** – Mainstay of treatment is sympathetic blockade and intravenous regional to facilitate physical therapy
- **Stanton-Hicks et al 1995** – Complex Regional Pain Syndromes I and II

Pain 1995;63: 127-133
Clinical features of CRPS

- Allodynia
- Altered sweating (absent, excessive, or reduced)
- Atrophy of skin with loss of wrinkles (glossiness of skin)
- Color changes of skin (cyanotic, erythematous, pale, or blotchy)
- Swelling
- Dupuytren's and other contractures
- Hair changes (excessive or reduced growth, and/or fineness instead of coarse)
- Inappropriate warmth or coldness
- Involuntary movements: tremor, dystonia, spasms
- Joint stiffness (acute or chronic arthritic changes)
- Muscle wasting and/or weakness
- Nails (brittle or clubbed; curved, thin, ridged)
- Osteoporosis: spotty, localized, or widespread
- Pigmentation changes
- Subcutaneous atrophy or thickening
Diagnostic Criteria for CRPS I

- Develops after an initiating noxious event or cause of immobilization
- Spontaneous pain or allodynia/hyperalgesia, is not limited to the territory of a single peripheral nerve, and is disproportionate to the inciting event
- There is or has been evidence of (1) edema (2) skin blood flow abnormality (3) or abnormal sudomotor activity
- The diagnosis is excluded by the existence of conditions that would otherwise account for the degree of pain and dysfunction

Merskey H & Bogduk N IASP Press; 1994
Validation of IASP Diagnostic Criteria

- Concerns about Sensitivity and Specificity
- 117 patients meeting criteria for CRPS and 43 patients with other known neuropathic pain
- Sensitivity (.98), Specificity (0.36) resulting in a correct diagnosis in 40% of cases

Pain 1999;81: 147-154
Making the clinical Diagnosis

1. Continuous spontaneous regional pain I that is disproportionate to the inciting event
2. There is no other diagnosis that better explains the signs and symptoms
3. Both the symptoms and signs are evaluated under 4 categories that include: sensory, vasomotor, sudomotor/edema, and motor/trophic

Pain Medicine 2007;8(4):326-331
Must Report 3 of the 4 symptom Categories

- **Sensory** – reports allodynia, hyperesthesia
- **Vasomotor** - reports temperature and/or skin color changes/asymmetry
- **Sudomotor/edema** - reports edema and/or sweating changes/asymmetry
- **Motor/trophic** - reports decreased range of motion, and/or weakness, tremor, dystonia. Trophic changes in hair, nail, or skin
Must Display at Least One sign in Two or More Categories

- **Sensory** – hyperalgesia to pinprick, Pain on light touch, temperature, pressure
- **Vasomotor** – Skin temp >1°C or color asymmetry
- **Sudomotor/Edema** – sweating asymmetry
- **Motor/Trophic** – Document decreased range of motion, weakness, tremor, dystonia. Note hair, nails, skin
<table>
<thead>
<tr>
<th>Criteria</th>
<th>Sensitivity</th>
<th>Specificity</th>
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</thead>
<tbody>
<tr>
<td>2 sign categories &amp; 2 sympt categories</td>
<td>0.94</td>
<td>0.36</td>
</tr>
<tr>
<td>2 sign categories &amp; 3 sympt categories</td>
<td>0.85</td>
<td>0.69</td>
</tr>
<tr>
<td>2 sign categories &amp; 4 sympt categories</td>
<td>0.70</td>
<td>0.94</td>
</tr>
<tr>
<td>3 sign categories &amp; 2 sympt categories</td>
<td>0.76</td>
<td>0.81</td>
</tr>
<tr>
<td>3 sign categories &amp; 3 sympt categories</td>
<td>0.70</td>
<td>0.83</td>
</tr>
<tr>
<td>3 sign categories &amp; 4 sympt categories</td>
<td>0.86</td>
<td>0.75</td>
</tr>
</tbody>
</table>

Pain 1999;81: 147-154
Chronic Stages

- Demineralized bone
  - diffuse and spotty distal distribution
  - peri-articular of longer bones

- Sudeck’s dystrophy

- Sensitivity of 73%
- Specificity of 57%

Pain Med 2006;7(S1): 64-96
- **Triple phase bone scan**
- 99m Tc-labeled Org phos
- Phase I (30 sec post injection): inc or dec uptake
- Phase II (blood pool, at 2min): periarticular hot zones assoc with long-term vasoconstriction
- Phase III (3 hours): mineralization phase, again periarticular uptake and metatarsal & metatarsalphalageal bones
- **Significant changes in acute and subacute periods**
- Sensitivity 97%
- Specificity 86%

Pain Med 2006;7(S1): 64-96
Epidemiology Study of CRPS I in Olmsted County

- Incidence: 5.46/100,000 person/yr
- Period Prevalence: 20.57/100,000
- Female/male: 4/1
- Median age of onset: 46
- Upper/lower extremity: 2/1
- Fracture most common etiology: 46%
- 74% spontaneous resolution

2009;259(25):273-280
Incidence: 26.2/100,000 person-yrs
Female/Male: 3.4/1
Age of peak incidence: 61-70 years
Upper extremities 59% of cases
Fracture most common cause: 44%

Pain 2007;129: 12-20
Associations with CRPS I

- **Migraine** (OR: 2.43 95% CI: 1.18-5.02)
- **Osteoporosis** (OR: 2.44 95% CI: 1.17-5.14)
- **Previous Neuropathies** (OR: 5.7 95% CI: 1.8-18.7)
- **Asthma** (OR: 3.0 95% CI: 1.3-6.9)
- **Menstrual Cycle Abnl.** (OR: 2.6 95% CI 1.17-5.14)
- **No association with previous psychopathology**

M. De Mos Pain 2009;139:458-66
Animal Models
Ischemia-reperfusion Model of CRPSI/RSD. Pain 2004;112:94-105
Deep tissue injury

Acute inflammation with edema

Normal healing

Compartment-like syndrome

Microvascular I-R injury

Vasospasm

Slow flow/no-reflow

Deep tissue ischemia

Chronic inflammation

Muscle/bone

Nerve

Nociceptor activation & sensitization

Nociceptor ectopic discharge

Central sensitization, Pain, Allodynia, Hyperalgesia

CRPS-II: Neurovascular bundle injury

CPI/CRPS-I

① Critical events for initiation

② Critical events for maintenance
Human Studies
Pathology of Skeletal Muscle and Peripheral Nerve in CRPS-I

- N=8 patients with severe loss of limb function +/- infections
- AKAs done light and Ems performed
- A loss of c-fibers (sural nerve) in 4 patients
- Soleus & Gastrocnemius muscles demonstrated: (1) Atrophic fibers and reduced type I fibers (2) Increased lipofuscin (3) Capillary basal membrane thickening and necrosis
- Microangiopathy similar to diabetes

Neurology 1998;51:20-5
Dramatic Loss of Vascular Integrity in the digit and forearm

- PECAM staining of superficial capillaries and pre capillary arterioles
- Hoechst staining of cell nuclei increased dispersion surrounding disrupted vessel.

Pain 2006;120: 244-266
Increased Skin Lactate in CRPS

Neurology 2000;55(8):1213-1215
Salivary Oxidative Profile in CRPS-I

Superoxide dismutase, uric acid, total oxidative status (metmyoglobin)

Pain 2008;138:226-232
Oxidative Stress in CRPS

- Zollinger PE (Lancet 1999 354:2025-2028), randomized control trial in using prophylactic vitamin C (500 mg) to scavenge hydroxyl radicals during wrist fracture. 52 patients in control and 63 in treatment group, with a 22% occurrence of CRPS in control vs 7% in treatment group.

- DMSO and N-acetylcysteine may reduce symptoms in warm and cold CRPS I (Pain 2003;102:297-307)
Dysfunctional SNS

- Plasma catecholamine levels are lower in CRPS affected limbs
- Laser-Doppler flowmetry studies fail to real constant SNS hyperactivity
- No histochemical evidence of an atypical distribution of sympathetic fibers in hyperalgesic human skin
- Alpha-1 receptors are increased in hyperalgesic skin

1. Sympathetic postganglionic neuron sprouts around the DRG stimulated by cytokines from glia

2. Alpha expression of primary afferents that can respond to postganglionic sympathetic neurons

Peripheral Inflammation

Blood Cytokine Levels

- IL-2 elevated
- IL-10 and TGFα1 were reduced
- Pro-inflammatory profile
- N=40, median disease duration of 3 months

Pain 2007;132:195-205
Blood Cytokine mRNA Levels

- Increased levels of TNF and IL-2
- Low levels of IL-4, IL-10 and IL-8
Central Inflammation

CSF Pro-Inflammatory Cytokines

• Glial cells implicated in neuropathic pain syndromes
• Regulate glutamate/aspartate
• Microglia are most important sources of cytokines in the CNS

• IL-1 and IL-6 are elevated not TNF
• IL-6 correlated with disease duration
• N=24

Aberrancies in Neurotransmitters in CRPS

- Markedly elevated plasma 5-HT (Anesth Analg 2008;106:1862-7)
- Increased peripheral releasability of neuropeptides via axon reflexes (Pain 2001;91:251-257)
- Increased risk of CRPS with ACE inhibitors (OR 2.7:1.1-6.8), via blocking catabolism of substance P and bradykinin (Pain 2009)
# QST Studies in CRPS

<table>
<thead>
<tr>
<th>Sensory Abnormality</th>
<th>Frequency %</th>
<th>Inferred Mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Warm hypoesthsia</td>
<td>20-30</td>
<td>Loss of C-fibers</td>
</tr>
<tr>
<td>Cold hypoesthsia</td>
<td>14-75</td>
<td>Loss of A-δ fibers</td>
</tr>
<tr>
<td>Cold alldodynia</td>
<td>14-75</td>
<td>Loss of A-δ &amp; central inhibition</td>
</tr>
<tr>
<td>Warm alldodynia</td>
<td>14-55</td>
<td>Sensitization of C fibers</td>
</tr>
<tr>
<td>Mechanical alldodynia</td>
<td>75-100</td>
<td>A-β conducting</td>
</tr>
</tbody>
</table>

Kemler, M Anesthesiology 2000;93:718-27
Small-Fiber Axonal Degeneration

Pain 2006;120:235-243
CRPS upper Extremity

- Lack of epidermal & dermal innervation
- More Aβ in Meisnners corpuscles (curved arrows)

Pain 2006;120: 244-266
Dorsal horn Atrophy,
Autopsy of Left Lower extremity CRPS

Brain Imaging in Neuropathic Pain

No Distinct Pain Matrix or Allodynia Network

References
a: Petrovic et al., 1999
b: Witting et al., 2006
c: Becerra et al., 2006
d: Schweinhardt et al., 2006
e: Peyron et al., 1998
f: Dureux et al., 2006
g: Peyron et al., 2004
Systemic Complications in CRPS
Atypical Chest Pain

- Sensitization of the ICBN
- Evoked by lifting arm
- 94% UE CRPS

Pain Phys 2009;12:E29-E34
Cardiac

- 800 CRPS pt nl baseline EKG/ECHO
- Complaints are usually palpitations, syncope, presyncope
- **4.5 times more likely to be diagnosed with neurocardiogenic syncope (esp in lower ext CRPS)**
- Decreased HR variability, inc with orthostatic stress, inc SVR, dec CO

GI Manifestations

- Intermittent diarrhea 18%
- GERD 73%
- IBS 17%
- Constipation 41%
- Nausea 23%
- Vomiting 11%
- Dysphagia 18%

N = 270 CRPS patients

Other Systemic Effects

- Urol: Mainly with biLE CRPS, 25% with difficulty voiding or incontinence.
- Endocrine: 30% hypothyroid, 38% low serum cortisol related to HPA axis dysfunction
- Pulm: SOB in 16% of pts with 2 or more extremities with CRPS

Treatment
Sympathetic Blocks

- Long history for use for patients with inoperable critical limb ischemia
- Equally long history in CRPS/RSD may have vasospasm, increased SNS reflexes
Meta-Analysis of Pharmaceuticals for CRPS I Management

Mean Duration of Symptoms <12 mo

- Bisphosphonates: alendronate, clodronate, pamidronate
- NMDA Antagonists: ketamine, memantidine
- Analgesics/anti-convulsants: parecoxib, lidocaine/ gabapentin
- Vasodilators: tadalafil
- Radical scavanger: Mannitol

Mean Duration of Symptoms >12 mo

- Bisphosphonate
- NMDA analogs
- Calcitonin
- Steroids
- Analgetics
- Calcitonin
- NMDA analogs
- Bisphosphonate
- Vasodilators
- Anticonvulsive
- Radical scavenger

Sympathetic blocks in CLI

- Non-reconstructable one year limb survival (46%) with std Med therapy (J Vasc Surg 1999;30:236-44)
- Non-reconstructable one year limb survival (58-61 %) with either chemical or surgical sympathectomy (Cardiovasc Surg 1999;7:200-202)
LSB in CRPS/RSD

- New onset cases (no controls), seems to benefit 79% of patients (Pain 2003;103: 199-207) Similar to previous findings (J Hand Surg Am 1983;8:153-59).

- Chronic CRPS I/RSD Rx with Radiofrequency ablation of sympathetic chain; Out of 20 patients, 5 had excellent relief followed out to 5 mo-3 yrs post RF of the sympathetic chain (Reg Anesth 1995;20:3-12.)
Spinal Cord Stimulation

- Extensive European Literature for critical limb ischemia
- Extensive international experience for CRPS/RSD
### SCS and Severe Limb Ischemia

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Before ESCS</th>
<th>After ESCS</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Macrocirculatory</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic ankle/arm pressure index (%)</td>
<td>32 ± 14</td>
<td>37 ± 14</td>
<td>NS</td>
</tr>
<tr>
<td>Systolic toe pressure (mm Hg)</td>
<td>9 ± 16</td>
<td>10 ± 23</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Microcirculatory</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Skin capillary density (N/mm²)</td>
<td>12 ± 6</td>
<td>30 ± 5</td>
<td>P&lt;0.001</td>
</tr>
<tr>
<td>Skin capillary diameter (μm)</td>
<td>15.7 ± 1.8</td>
<td>15.5 ± 1.5</td>
<td>NS</td>
</tr>
<tr>
<td>Red cell velocity (mm/sec)</td>
<td>0.054 ± 0.014</td>
<td>0.762 ± 0.205</td>
<td>P&lt;0.001</td>
</tr>
<tr>
<td>Sodium fluorescein perfused capillaries (N/mm²)</td>
<td>20 ± 4</td>
<td>44 ± 5</td>
<td>P&lt;0.001</td>
</tr>
<tr>
<td>Sodium fluorescein appearance time (sec)</td>
<td>72.15</td>
<td>45 ± 9</td>
<td>P&lt;0.001</td>
</tr>
</tbody>
</table>

SCS in Non-reconstructable CLI


- Limb Salvage only impacted in patients with intermediate levels of microcirculation (TcpO2 10-30 mmHg)

- 78% 1 year limb survival vs 45% and 43% transitioned from Fontaine III/IV to I/II (Eur J Vasc Endovasc Surg 2003;26:280-286)
Fig. 3. Cumulative limb survival of the SCS-Match (solid line) vs SCS-No-Match (dashed line) vs No-SCS (hatched line) groups. The vertical lines A, B and C represent 3, 6 and 12 months, respectively. *p < 0.03.
Summary of SCS Studies in RSD/CRPS I

- Barolat et al. (n=18), prospective with 11 patients at least 50% or better Sterotact Funct Neurosurg 1989;53:29-39
RCT: SCS/PT vs PT

**Figure 1.** Mean (±SD) Scores for Pain Intensity in Patients with Reflex Sympathetic Dystrophy Who Were Assigned to Spinal Cord Stimulation plus Physical Therapy or to Physical Therapy Alone.

The intensity of pain was measured on a visual-analogue scale from 0 cm (no pain) to 10 cm (very severe pain). Data are from the intention-to-treat analysis.

<table>
<thead>
<tr>
<th>Age</th>
<th>Sex</th>
<th>Source of injury</th>
<th>Pain Site</th>
<th>Diagnosis</th>
<th>SMP or SIP</th>
<th>PTSD</th>
<th>Symptom duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>21</td>
<td>M</td>
<td>Scorpion sting</td>
<td>Left foot</td>
<td>CRPS I</td>
<td>SMP</td>
<td>No</td>
<td>6 mo</td>
</tr>
<tr>
<td>28</td>
<td>M</td>
<td>Terrorist explosion and gun shot wound</td>
<td>Right shoulder</td>
<td>CRPS II</td>
<td>SIP</td>
<td>Yes</td>
<td>11 mo</td>
</tr>
<tr>
<td>34</td>
<td>M</td>
<td>Helicopter crash</td>
<td>Right knee</td>
<td>CRPS I</td>
<td>SMP</td>
<td>Yes</td>
<td>12 mo</td>
</tr>
<tr>
<td>23</td>
<td>M</td>
<td>Terrorist explosion</td>
<td>Left leg</td>
<td>CRPS II</td>
<td>SIP</td>
<td>Yes</td>
<td>10 mo</td>
</tr>
<tr>
<td>22</td>
<td>M</td>
<td>Terrorist explosion</td>
<td>Right leg</td>
<td>CRPS II</td>
<td>SMP</td>
<td>Yes</td>
<td>12 mo</td>
</tr>
<tr>
<td>27</td>
<td>M</td>
<td>Terrorist explosion</td>
<td>Bilateral legs</td>
<td>CRPS II</td>
<td>SMP</td>
<td>Yes</td>
<td>11 mo</td>
</tr>
<tr>
<td>45</td>
<td>F</td>
<td>Rib resection</td>
<td>R chest wall</td>
<td>CRPS I</td>
<td>SMP</td>
<td>No</td>
<td>11 mo</td>
</tr>
<tr>
<td>24</td>
<td>M</td>
<td>Terrorist explosion</td>
<td>Left ankle</td>
<td>CRPS II</td>
<td>SMP</td>
<td>Yes</td>
<td>12 mo</td>
</tr>
<tr>
<td>24</td>
<td>F</td>
<td>Sprain</td>
<td>Right ankle</td>
<td>CRPS I</td>
<td>SMP</td>
<td>No</td>
<td>9 mo</td>
</tr>
<tr>
<td>24</td>
<td>M</td>
<td>Motor vehicle crash</td>
<td>Right ARM</td>
<td>CRPS II</td>
<td>SMP</td>
<td>No</td>
<td>5 mo</td>
</tr>
</tbody>
</table>

Mean age 27 ± 7.4 yr; symptom duration before spinal cord stimulation 9.9 ± 2.5 mo.
SMP = Sympathetically maintained pain, SIP = sympathetically independent pain; PTSD = posttraumatic stress disorder.
Daily Mean Pooled Pain Numeric Rating Scale Pre-SCS, 3, and 6 Months Post SCS Implant

- NRS All Patients (n=10)
- NRS War Wounded (n=6)
- NRS CRPS II (n=6)

<table>
<thead>
<tr>
<th>Time</th>
<th>NRS All Patients</th>
<th>NRS War Wounded</th>
<th>NRS CRPS II</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre SCS</td>
<td>7.8</td>
<td>8.3</td>
<td>8.3</td>
</tr>
<tr>
<td>Post SCS 3 months</td>
<td>1.7</td>
<td>2.3</td>
<td>1.8</td>
</tr>
<tr>
<td>Post SCS 6 months</td>
<td>1.6</td>
<td>1.8</td>
<td>1.8</td>
</tr>
</tbody>
</table>
DRG Stimulation for CRPS

IV Ketamine
Double Blind RCT
4 day infusion

- 30 Patients treated
- 30 in control
- 22-30 mg/hr
- Significant pain reduction
- No functional improvement
- Mild psychomimetic effects, nausea, vomiting

Pain 2009;145:304-11
Outpatient serial IV Ketamine for 10 days Double Blinded RCT

- 19 treated, 10 controls
- 4 hours infusions
- 0.35 mg/kg/hr, max 100 mg in 4 hours
- Reductions in spontaneous, evoked and affective components

Pain 2009;147:107-115
Summary

- Recently established diagnostic criteria
- Complex pathophysiology
- Systemic complications recently appreciated
- Chronic condition with a high rate of disability.
- Evolving therapies