CRPS AND NEUROMODULATION

Romanth Waghmarae, MD, DABA, FIPP
Assistant Clinical Professor Anaesthesia & Pain – McMaster University
Editorial Board – American Journal of Pain Management & Pain

6245 Sheridan Drive, Suite 116
Williamsville, NY 14221
716-505-1500
OBJECTIVES

• Brief Overview of CRPS

• Brief Overview of Treatment Options

CRPS: THE CHALLENGE

“Of all the chronic neuropathic pain syndromes, none has perplexed patient, clinician, and scientist more than the complex regional pain syndromes (CRPS), heretofore known as reflex sympathetic dystrophy (RSD) and causalgia.”

Galer BS CRPS Chapter 20 Bonica’s Management of Pain 3rd Ed. Lippincott Williams &Wilkins 2001
CHALLENGES

1. NATURAL COURSE AND PATHOPHYSIOLOGY REMAINS POORLY UNDERSTOOD – hence CRPS I & II based on inciting event

2. INFLAMMATION, VASODYSREGULATION / AUTONOMIC DYSTONIA AND AXONAL INJURY ARE IMPLICATED IN THE PATHOGENESIS

3. THERAPEUTIC INTERVENTIONS REMAIN CONTROVERSIAL DUE TO THE LACK OF RCT's

4. DIAGNOSIS IS USUALLY MADE BY HIGH INDEX OF SUSPICION, EXAMINATION AND CAREFUL HISTORY AND EXCLUSION

5. THERE IS ASSOCIATED SIGNIFICANT MORBIDITY AND LOSS OF QOL INDICATORS

EPIDEMIOLOGY

• INCIDENCE – 26.2 PER 100,000 PERSON YEARS (Crps I > CrpsII)

• AGE – COMMON IN YOUNGER ADULTS --- MEAN 41.8, AGE AT INJURY 37.7 (CHILDREN 12.5)

• MEAN DURATION OF SYMPTOMS BEFORE SEEING A PAIN SPECIALIST 30MO

• 3.4 MORE FREQUENT IN FEMALES THAN MALES

• EARLY STAGE USUALLY INVOLVES SINGLE LIMB
A clinical diagnosis of CRPS can be made when the following criteria are met:

1. * Continuing pain that is disproportionate to any inciting event

2. * At least 1 symptom reported in at least 3 of the following categories:
   - Sensory: Hyperesthesia or allodynia
   - Vasomotor: Temperature asymmetry, skin color changes, skin color asymmetry
   - Sudomotor/edema: Edema, sweating changes, or sweating asymmetry
   - Motor/trophic: Decreased range of motion, motor dysfunction (e.g., weakness, tremor, dystonia), or trophic changes (e.g., hair, nail, skin)

3. * At least 1 sign at time of evaluation in at least 2 of the following categories:
   - Sensory: Evidence of hyperalgesia (to pinprick), allodynia (to light touch, temperature sensation, deep somatic pressure, or joint movement)
   - Vasomotor: Evidence of temperature asymmetry (>1°C), skin color changes or asymmetry
   - Sudomotor/edema: Evidence of edema, sweating changes, or sweating asymmetry
   - Motor/trophic: Evidence of decreased range of motion, motor dysfunction (e.g., weakness, tremor, dystonia), or trophic changes (e.g., hair, nail, skin)

4. * No other diagnosis better explaining the signs and symptoms

IASP Modified Criteria
IF 2 OUT OF 4 SIGNS ARE PRESENT AND 3 OUT 4 SYMPTOMS ARE PRESENT THEN

Sensitivity was 0.85 and the specificity was 0.69 for a clinical diagnosis of CRPS (2007-Budapest Group Meeting of 2003)

This has been fairly accurate clinically in diagnosing CRPS and reducing the high false positive rates associated with the original 1994 criteria (over diagnosis)

Higher specificity is required to meet research criteria, so the recommendation that 2 of the 4 sign categories and all 4 symptom categories must be positive for the diagnosis to be made in a research setting, results in a sensitivity of 0.70 and specificity of 0.94.

Due to this 15% of patient previously diagnosed with CRPS will be excluded even if they fulfill the original 2003, 1997 criteria – Hence a new category of CRPS - NOS
PATHOPHYSIOLOGY

- **Peripheral and Central Sensitization**: involves algogenic substances, SP and CGRP instigate anterograde and retrograde actions with recruitment of other cell types as well as involvement of WDR’s and second order neurones.

- **SMP** – defined as an underlying mechanism in a subset of patients with neuropathic pain. SMP is not a clinical entity per se. Nor is it a sine qua non for CRPS as was previously believed. (Stanton-Hicks M, Janig W, Hassenbusch S, Haddox JD, Boas R, Wilson P. Reflex sympathetic dystrophy: changing concepts and taxonomy. *Pain*. Oct 1995;63(1):127-33)

- **Sensory and Motor Dysfunction** - peripheral and central sensitization explains the pathophysiology of spontaneous pain and hyperalgesia. Similar mechanisms involving abnormalities of CNS motor processing of muscles and abnormalities of visual and sensory integration resulting in tremors (>50%). (Deuschl, Blumberg S, Jensen M. Tremor in reflex sympathetic dystrophy. *Arch Neurol*. 1999;48:1247-1252)

- **Aberrant healing and exaggerated inflammation** – SP, CGRP & Pronociceptor mediators in tissue

CRPS: A web-based survey

Inciting event

- Fracture 15.1%
- Sprain 11.1%
- Crush Injury 10.4%
- Surgery 29.3%
- Others 34.1%
  (Contusion, Stroke, Dislocation, MVA, Electrical Injury, Injection)

Factors associated with increased pain

- Physical stress
- Emotional stress
- Hot weather
- Cold weather
- Lying down
- Moving the affected area
- Working

SPREAD OF SYMPTOMS

• 77% reported spread of symptoms to site other than the initial location

• Exact spread of CRPS not known in Literature

• Independent spread known to occur in 6.7% of CRPS I cases

• Investigators agree that spread id not uncommon

Diagnostic considerations CNS

Brain (stroke, neoplasm, encephalitis)
Spinal cord (trauma, transverse myelitis, either structural or tumor-related syringomyelia)
Tabes dorsalis
Multiple sclerosis
Poliomyelitis

Radiculopathy
Structural (eg, due to structural impingement of a diskal, osteophyte-, or tumor-related nature)
Metabolic (eg, diabetes, vasculitis infectious)
Neoplastic

Neuropathy
Focal
   Diabetes
   Inflammatory or infectious (Lyme), sarcoid
   Posttraumatic
   Entrapment (eg, carpal tunnel, cubital tunnel)
   Toxic
   Neoplastic (neuroma)
Multifocal (mononeuritis multiplex)
   Diabetes
   Vasculitis
   Infectious
   Toxic
Bilateral or diffuse
   Diabetes
   Alcohol
   Nutritional
   Guillain Barre syndrome or chronic inflammatory demyelinating polyneuropathy
   Porphyria
Plexopathy
- Infectious
- Autoimmune/idiopathic
- Tumor (primary or secondary neoplasm), especially Pancoast syndrome
- Trauma (macro or cumulative)
- Entrapment (thoracic outlet syndrome)

Vascular disorders
- Raynaud phenomena
- Peripheral atherosclerotic disease
- Arterial insufficiency
- Phlebothrombosis

Monomelic amyotrophy

Psychological
- Hysteria
- Somatoform disorder, including malingering

Movement disorders
- Metabolic or systemic (eg, renal failure, amyloidosis)
- Autoimmune or rheumatological disorder
- Infectious (eg, viral, fungal, Lyme) iatrogenic (eg, prescribed medication)
- Demyelinating (CIDP, paresis or sensory deficiency due to multiple sclerosis)
- Toxic exposure (eg, vinca alkaloids, heavy metals)
WORKUP---NO SPECIFIC TEST/S CONFIRM THE DIAGNOSIS

- **LAB Studies:** Blood work – CBC, ESR, CRP, ANA, RA, CFP, Immune studies, Bone Scan, Hb A1C
  
  EMG / sensory NCV – to define nerve issues, c fiber function

- **Vascular Studies**

- **Imaging studies:** Radiography: In the chronic stages of CRPS, plain radiographs may reveal endosteal and intracortical excavation, resorption of subperiosteal and trabecular bone, localized bone demineralization, and/or osteoporosis


  **MRI:** Sensitive less specific – joint effusion, swelling soft tissue

- **Other studies:** Quantitative Sensory Testing – removes subjectivity

  Autonomic Function Testing – thermography, QSART, TST, laser Doppler flow

  Neurogenic Inflammation – proinflammatory mediators and vasoactive elements – interleukin 6, tryptase, TNF alpha, endothelin 1

  Skin, Muscel, Nerve biopsies
PHARMACOTHERAPY

- **Steroids** – used early effective 60-80mg/day instituted within 2mo of the inciting event
- **Calcium Regulating agents** – intranasal calcitonin reduces pain, Intravenous (IV) clodronate (300 mg daily) and alendronate (either 7.5 mg/d IV or 40 mg/d orally) have been shown to significantly improve pain, swelling, and range of movement in patients with acute CRPS ---- mechanisms unkown
- **Opioids & NASID’s** – No studies done , used as part of treating pain
- **TCA’s & SSRI’s/SNRI’s** – has been beneficial in DPN & PHN – no studies in CRPS
- **IV Lidocaine** – no controlled studies some efficacy reported – Mexilitene, Patch
- **GABA Agonists** – no studies on effects on pain, Intrathecal Baclofen useful in dystonia
- **Calcium Channel Modulators** – Gabapentin, Pregabalin – mildly beneficial in CRPS
- **Beta Blockers** – some reports state benefit – no studies.
- **Oral Sympatholytics** – in theory would be effective – side effect profiles too high.
- **Clonidine** – no controlled long term trials, case reports show benefit, new gel may show promise
INTERVENTIONAL PROCEDURES

- **Sympathetic Blocks** – Specific/IV – 70% of patients report some form of response – no studies on long term benefits, techniques have been studied.

- **IV Regional sympathetic Block** – Guanethidine (7 controlled studies no benefit), Bretyllium, --- ?effects of Tourniquet on A-β and A-δ fiber conduction.

- **IV Phentolamine** – may have benefit superior to stellate block – not fully studied

- **IV Ketamine** – Most promising to date - 66-80% patients showed an overall improvement as measured by increased function, reduced medication requirements, or both (Correll GE, Maleki J, Gracely EJ, Muir JJ, Harbut RE. Subanesthetic ketamine infusion therapy: a retrospective analysis of a novel therapeutic approach to complex regional pain syndrome. *Pain Med.* Sep 2004;5(3):263-75)

- **IV Immunoglobulin** – postulated thru effects of astrocytes and microglia production of cytokines

- **Epidural Clonidine** – effective but side effect profile very high

- **Surgical Sympathectomy** – not suggested routinely, seems to have benefit if done within the first 12 mo, most symptoms reappear after successful sympathectomy

- **Physiotherapy** – essential for eventual successful outcome

- **Psychotherapy**
DIAGNOSIS AND MANAGEMENT OF COMPLEX REGIONAL PAIN SYNDROMES
Treatment algorithm for complex regional pain syndromes.

- Diagnosis CRPS
- Start treatment as early as possible

- Psychological pathway
  - Pain coping skills
  - Biofeedback, relaxation training
  - Cognitive-behavioral therapy

- Rehabilitation pathway
  - Respect pain threshold. The therapy must not hurt!
    - Pain management (anticonvulsants, antidepressants, opioids, topicals)
    - Physiotherapy
    - Interventional pain management (sympathetic blocks)

- Acute stages with inflammatory component (edema)
  - Corticosteroids

- Treatment adapted to degree of severity

- Severity of CRPS
  - Intense pain at rest and during movements
    - Intense pain management
    - Immobilization
    - Contralateral physiotherapy
    - If SMP-sympathetic blocks

- Moderate
  - No pain at rest but pain during movements
    - Pain management
    - Physiotherapy and occupational therapy up to pain threshold

- Mild
  - No pain at rest and no pain during movements
    - Intense physiotherapy and occupational therapy

- Relapse
- Repeat pathway

- Neurostimulation (e.g., spinal cord stimulation)
  - Epidural clonidine
1962 – Mazars (France) used SCS for severe neuropathic pain – based on theory of Head & Holmes - “epicritic and protopathic afference” of chronic pain

1965 (Science) -- Melzack & Wall – Gating Theory at first spinal relay--Selective activation of large fibers

1967 -- Shealy - First report of electrical stimulation of spinal cord. 80 % benefit – Sweet – worst results (back pain)-- Focus was on psychological selection not type of pain

1969 – Reynolds - Descending pathways from PAG -

1973 -- Bonica – First meeting

1975 – IASP – SCS Selective action on neuropathic pain not nociceptive pain

1977 – Richardson & Akil PAG stimulation

1980's – Not effective in nociceptive forms of pain

1985's – awareness that SCS is effective for neuropathic pain, PVD, Angina

1990-93—Tsubokawa Motor Cortex Stimulation – based on concept of attenuation of Brain Stem

The Paths of Pain - IASP
NEUROMODULATION – (SCS) CONTD

Improvements in technology, techniques, electrical selectivity have increased the use of SCS – further understanding of SCS

Accepted mode of Action:

- Activation of low threshold, large fibers
- Decrease in excitatory amino acid release (Glutamate)
- Enhancement of GABA inhibitory system ($\text{GABA}_\beta$)
- Increase release of Adenosine, Serotonin and Norepinephrine
# SCS – Indications and Expected outcomes

<table>
<thead>
<tr>
<th>Success &gt;Failure</th>
<th>Success &gt;Failure</th>
<th>Variable Success</th>
<th>Failure &gt;Success</th>
<th>Failure &gt;Success</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Angina Pectoris</strong></td>
<td>CRPS 1 &amp; 2</td>
<td>Amputation-Phantom Limb</td>
<td>Perianal/Genital</td>
<td>Central post-stroke</td>
</tr>
<tr>
<td><strong>PVD: Vasospastic</strong></td>
<td>Peripheral nerve damage</td>
<td>Intercostal Neuralgia</td>
<td>Partial cord lesion</td>
<td>COMPLETE CORD LESION</td>
</tr>
<tr>
<td><strong>PVD: Occlusive</strong></td>
<td>Diabetic neuropathy</td>
<td>Postherpetic neuralgia</td>
<td></td>
<td>Complete root avulsion</td>
</tr>
<tr>
<td></td>
<td>Brachial plexus damage</td>
<td>Low Back Pain</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Lumbosacral/Cervical Rhizopathy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cauda Equina</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Amputation-Stump Pain</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

IASP-World Pain Congress – Sydney 2005
CRITERIA FOR SUCCESS

Neuropathic Pain:

1995 – Lazorthes --- 152/132 (90%) 2-20 yrs outcomes positive – peripheral nerve injury

1989 – Barolat – 18/9 CRPS -1 – good relief

2004 – Kemler -54/36 CRPS-1 – good benefit

1982 – Broseta – 70% - CPRS – 2 – excellent outcomes

Factors:

- Time between symptoms – diagnosis – SCS
- Severity of symptoms at time of SCS
- Stage of pathology at time of SCS
- Patient expectations of SCS

IASP-World Pain Congress – Sydney 2005
NEUROMODULATION

- Both SCS and PNS have been used in CRPS. SCS may be considered for CRPS type I, while PNS is considered a treatment for CRPS type II, providing relief from pain that is limited to the distribution of a major nerve (Ghai and Dureja, 2004). A review of the literature indicates that there is some evidence that these procedures can reduce pain in patients with CRPS.

- SCS for CRPS type I, based on the evidence, this treatment appears to be effective ((Cruccu, et al., 2007)—Grade A (Grade D for CRPS II)

- SCS for CRPS II, the available evidence is positive but it requires confirmatory comparative trials before the use of SCS can be unreservedly recommended in these conditions ((Cruccu, et al., 2007)

- Cochrane Review on 2 studies done (Mailis-Gagnon, et al., 2004), there is limited evidence that spinal cord stimulators are effective for some types of chronic pain (i.e., failed back syndrome and CRPS type I) and that patient selection should be thorough and indications for SCS need to be clear before treatment is provided.

- Clinical and cost-effectiveness and predictors of SCS outcome (Taylor, et al., 2006)- concluded that SCS appears to be an effective therapy in the management of patients with CRPS type I and type II
Kumar – Neurosurgery 2002----- 4 studies in total
UK Neuromodulation Society Statement:

CRPS patients respond well to early intervention with SCS

International Guidelines for the treatment of CRPS developed under the auspices of the International Association for the Study of Pain (IASP), recommends SCS for CRPS at 12-16 weeks


Lack of RCTs does not equate to a lack of effectiveness and the literature on SCS should be considered as a body rather than RCTs in isolation
# Neurostimulation: Reduction in Pain

<table>
<thead>
<tr>
<th>Reference</th>
<th># of Patients</th>
<th>Mean Follow-up</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>North</td>
<td>171</td>
<td>7 years</td>
<td>52% with ≥ 50% relief</td>
</tr>
<tr>
<td><em>Pain</em>, 1993</td>
<td>64</td>
<td>4 years</td>
<td>55% good to excellent relief</td>
</tr>
<tr>
<td><em>Neurosurgery</em>, 1995</td>
<td>39 study meta analysis</td>
<td>16 months</td>
<td>59% with ≥ 50% relief</td>
</tr>
<tr>
<td>De La Porte</td>
<td>24</td>
<td>19 months</td>
<td>78% good to very good effect</td>
</tr>
<tr>
<td><em>Pain</em>, 1993</td>
<td>111</td>
<td>5.6 years</td>
<td>59% good to excellent results</td>
</tr>
<tr>
<td>Segal</td>
<td>70</td>
<td>1 year</td>
<td>55% with ≥ 50% relief</td>
</tr>
<tr>
<td><em>Neurol Research</em>, 1998</td>
<td>Multi-center</td>
<td>5.6 years</td>
<td>59% good to excellent results</td>
</tr>
<tr>
<td>Burchiel</td>
<td>70</td>
<td>1 year</td>
<td>55% with ≥ 50% relief</td>
</tr>
<tr>
<td><em>Spine</em>, 1996</td>
<td>Multi-center</td>
<td>5.6 years</td>
<td>59% good to excellent results</td>
</tr>
<tr>
<td><em>Surg Neurol</em>, 1991</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
# Reduction in analgesic consumption

<table>
<thead>
<tr>
<th>Reference</th>
<th># of Patients</th>
<th>Mean Follow-up</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ohnmeiss</td>
<td>40</td>
<td>2 years</td>
<td>66% decreased eliminated narcotics</td>
</tr>
<tr>
<td><em>Spine, 1996</em></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>North</td>
<td>171</td>
<td>7 years</td>
<td>58% reduced/eliminated analgesics</td>
</tr>
<tr>
<td><em>Neurosurgery, 1995</em></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>De La Porte</td>
<td>64</td>
<td>4 years</td>
<td>90% reduced medication</td>
</tr>
<tr>
<td><em>Pain, 1993</em></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kumar</td>
<td>111</td>
<td>5.6 years</td>
<td>59% satisfactory relief</td>
</tr>
<tr>
<td><em>Surg Neurol, 1991</em></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Racz</td>
<td>26</td>
<td>1.8 years</td>
<td>81% reduced/eliminated narcotics</td>
</tr>
<tr>
<td><em>Spine, 1989</em></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Segal</td>
<td>24</td>
<td>19 months</td>
<td>59% satisfactory relief</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
TREATMENT OUTCOMES

• Mode of therapy/Nature of Pathology/Patients age/Time to diagnosis

Good prognosis if onset between ages 2-22yrs, (prognosis poor if related to surgical procedure)

Delay in diagnosis results in less than adequate responses

Type of therapy introduced when diagnosis made is a strong predictor
TREATMENTS RECEIVED PRIOR TO REFERRAL TO TERTIARY CARE CENTER

CLINICAL EXPERIENCE

- Post traumatic MVA Sternal Fracture Pain
- PVD with Ulcers awaiting possible amputation
- Neurogenic Claudication in patient poor surgical risk
- Post Amputation stump pain
- Occipital neuralgia
- Intercostal Neuralgia
- Interstitial Cystitis
- Pelvic endometriosis
- Ilioinguinal neuralgia
- Angina Patient died two days before trial