What is Complex Regional Pain Syndrome? Diagnosis and Management

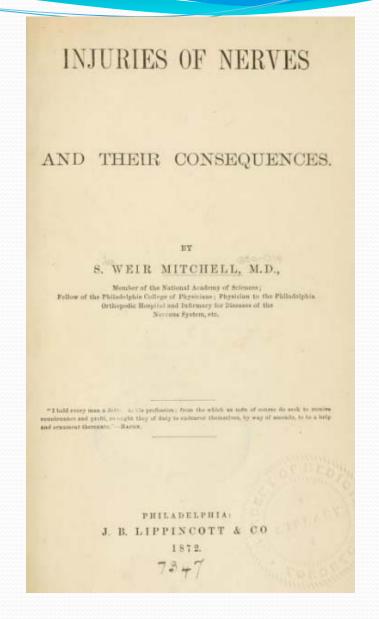
Samyadev Datta, MD, FRCA Director, Center for Pain Management Associate Professor, Anesthesiology, Rutgers University Hackensack, NJ 07601 201 488 7246

Disclosure

Consultant board Quest diagnostics

Causalgia

- Described in Union Veterans of the Civil war following traumatic nerve injuries
- Acute and chronic regional pain condition with a unique burning quality to the pain
 - Affected 10% of wounded soldiers with traumatic peripheral nerve injuries in the distal extremity
 - "Burning pain"
- Vasomotor/sudomotor changes
- Allodynia, hyperalgesia and psychological sequelae
- Syndrome sometimes resolved in weeks or months
 - Some patients had persistent pain when re-evaluated more than 25 years after the injury



Mitchell, Lippencott 1872

Complex Regional Pain Syndrome

- Defined inflammatory and neuropathic pain disorder principally characterized by involvement of the autonomic nervous system.
- Type I: without obvious nerve damage (reflex sympathetic dystrophy)
- Type II: with obvious nerve damage (causalgia)

Epidemiology

- Mean age 36-42 years
- Female to male ratio 4:1
- Incidence
 - CRPS I 5.46 per 100,000 person-years
 - CRPS II 0.82 per 100,000 person-years
- Upper limb affected twice as commonly as lower limb
- Antecedent events
 - Fracture (46%)
 - Strain or sprain (10-29%)
 - Post-surgery (3-24%)
 - Contusion or crush injury (8%)
 - Unknown causes (2-17%)

Allen G, et al. Pain 1999;80(3):539-44 Sandroni P, et al. Pain 2003;103(1-2):199-207

Differential Diagnosis

- Peripheral neuropathy
- Focal or entrapment neuropathies
- Vasculitis
- Scleroderma
- Focal joint inflammatory disease
 - Gout

- Vascular abnormalities
 - DVT
 - Thrombophlebitis
 - Arteriovenous fistulae
- Progressive systemic sclerosis
- Disuse atrophy
- Lymphedema

Budapest Criteria 2003

- Pain continuing that is disproportionate to the any inciting event
- No other diagnosis can better explain the signs and symptoms

Table 1: Clinical Diag	nostic Criteria for CRPS
Must Report at Leas	t One Symptom In 3 of the 4 Following Categories
Sensory	Hyperesthesia and/or Allodynia
Vasomotor	Temperature Asymmetry and/or Skin Color Changes and/or Skin Color Asymmetry
Sudomotor/Edema	Edema and/or Sweating Changes and/or Sweating Asymmetry
Motor/Trophic	Decreased Range of Motion and/or Motor Dysfunction (Weakness, Tremor, Dystonia) and/or Trophic Changes (Hair, Nail, Skin)
Must Display at Leas	st 1 Sign at Time of Evaluation in 2 or More of the Following Categories*
Sensory	Evidence of Hyperalgesia (to Pinprick) and/or Allodynia (to Light Touch and/or Deep Somatic Pressure and/or Joint Movement)
Vasomotor	Evidence of Temperature Asymmetry and/or Skin Color Changes and/or Asymmetry
Sudomotor/ Edema	Evidence of Decreased Range of Motion and/or Motor Dysfunction (Weakness, Tremor, Dystonia) and/or Trophic Changes (Hair, Nail, Skin)
* A Sign Is Counted of	only If It Is Observed at Time of Diagnosis

Pathophysiology

- Mechanisms are poorly understood
 - Small fiber neuropathy
 - Sympathetic nervous system dysfunction
 - Peripheral and central nervous system inflammation
 - Central sensitization
 - Central nervous system reorganization

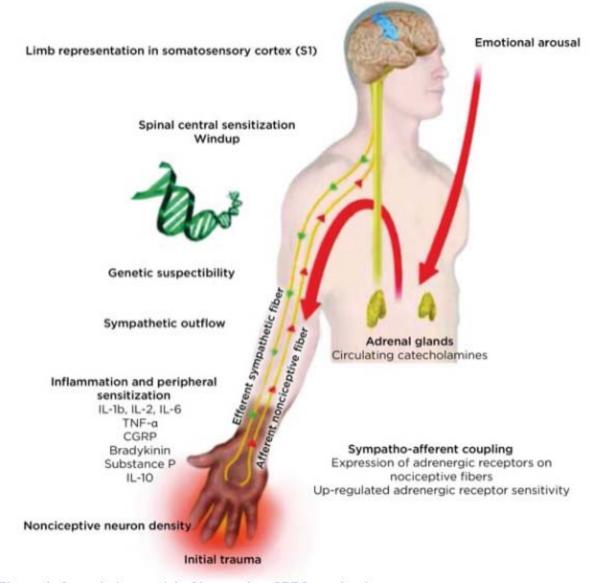


Figure 1. Speculative model of interacting CRPS mechanisms.

CGRP, calcitonin gene-related peptide; CRPS, complex regional pain syndrome; IL, interleukin; TNF, tumor necrosis factor

Gharibo 2014

Sensory Manifestations

- Pain
 - Characteristically disproportionate in intensity to the inciting event
 - Often felt distally in the affected extremity
 - Increased with limb in dependent position
- Hyperesthesias
 - Stimulus evoked
 - No consistent relationship to individual nerve territories or to the site of inciting lesion
 - Mechanical (pinprick)
 - Motion-dependent amplification of pain
 - Central sensitization
 - Thermal
 - Peripheral sensitization

Movement Abnormalities

- Weakness
 - All muscles of the affected extremity
 - Small, accurate movements are characteristically impaired
 - Nerve conduction and EMG studies are normal except in very chronic stages
- Reduced range of motion
 - Edema related in acute stage
 - Fibrosis and contracture related in chronic stage
- Tremor
 - Postural or action tremor
- Myoclonus
 - Almost twice as common in CRPS II than in CRPS I
- Dystonia
 - distal dystonia
 - Potentially spreads to other limbs

Autonomic Signs and Symptoms

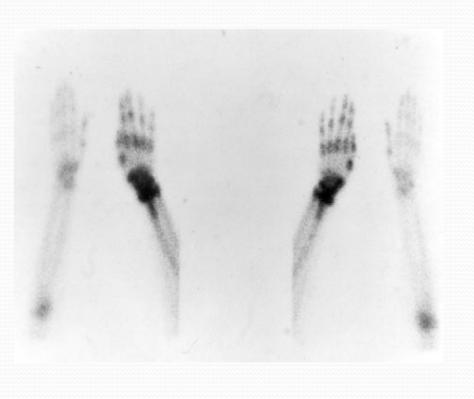
- Edema (81%)
 - Distally on the affected limb
 - Often diminishes after sympathetic block
- Temperature and color variation (56%)
 - Red and hot in acute stages
 - Bluish and cold in chronic stages
 - Often a difference of more than 1°C
 - May change within minutes depending on thermoregulatory condition
- Sweating abnormalities (50%)
 - Hyperhidrosis more frequently

Trophic Signs and Symptoms

- Abnormal hair and nail growth
 - Appear several days after the onset of symptoms
- Atrophy of the skin
- Muscle atrophy
 - Accompanied by fibrosis and contracture
- Osteoporosis
 - Particularly in chronic stages

Three-Phase Bone Scintigraphy

- Can reveal focal subchondral or subperiosteal osteoporosis
- Pathological uptake in metacarpophalangeal joints and metacarpal bones in phase three ("mineralization phase") described as highly sensitive and specific
- Only positive for significant changes during the subacute period (up to one year)
- No known gold standard against which to compare this test



Management guidelines.

- ❖ Basic goal is control of pain and maintain function
- Functional improvement may happen before pain control
- There are no best practices; guidelines are based on best clinical evidence
- ❖ There is no specific test to diagnose the condition
- ❖ There is no cure for this condition

*	Symptoms may be in remission for variable durations
*	Early intervention results in better results
*	Education of health care providers allows for early recognition & intervention
*	Be willing to believe patients and refer to specialists sooner rather than later
*	Multidisciplinary approach has the best results

Perioperative Management of Patients with CRPS

Preventive Measures

- Wait till symptoms subside
- Decrease operative and tourniquet times
- Minimal invasive surgery
- Adequate pain control
- Early Post-op functional mobilization
- High dose vitamin C
- No advantage in GA vs Regional, however most favor regional for the dense pain relief post-op
- Ketamine periop
- Preop sympathetic blockade

Intra/Post-operative

- Alpha 2 agonists show promise
- Ketamine infusion
- Gabapentin
- Epidural clonidine
- Dexmedetomidine
- Peripheral nerve catheters
- Physical rehab
 - Desensitization techniques
- Multi-modal analgesia

Rogers et al. 2008

Assad & Glass 2012

Medication Categories

No particular category has been more useful, rather a combination is better tolerated.

Anti inflammatory: They are all the same and have similar side effects.

- Cox-2 inhibitors may have a better side effect profile. NSAID class of medications may also be used in acute exacerbation of symptoms.
- I prefer a 5-7 day course of high dose celecoxib (400mgs per day)/Ibuprofen 800mgs tid for 3-5 days

Neuropathic Medications

- Gabapentin, (Neurontin) start at about 100-300 at night time and titrate. Max dose is 2400mgs/day.
- Gralise is long acting gabapentin. Uses gastro retentive technology
- Pregabalin (Lyrica) start at 50-100mgs at night and then titrate. Max daily dose is 600mgs. Average daily dose is about 200mgs
- Amitriptyline , Nortriptyline
- Duloxetine (Cymbalta), Milnacipran (Savella)

- Anti-convulsants have been used extensively.

 Oxcarbazepine,(Trileptal), Levetiracetam (Keppra)
- ❖ Muscle relaxants: Dystonia is a documented feature in CRPS. Use of baclofen helps. Benzodiazepines are very difficult to wean from.
- ❖ Na channel blockers including topiramate
- Anxiolytics: Do not have analgesic action but help manage some symptoms
- ❖ Antidepressants may have some analgesic action.
- Calcium channel blockers
- Calcitonin works by activating the calcitonin receptors that have an antihyperalgesic effects.

- ❖ Opioids are not preferred drug of choice but may be used to try and control pain in the initial phase.
 - ❖ Also remember that opioids may cause glial cell activation that may magnify neuropathic symptoms.
- ❖ Central sensitization is a big issue in CRPS and opioids increase central sensitization.
- Short acting opioids may be helpful but try to avoid long-term opioids.

Stellate Ganglion nerve block.

Usually around the C6 vertebra.

Needs to be done under fluoroscopy.

High risk of vascular injections.

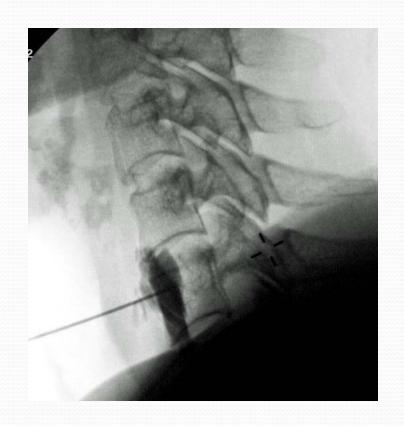
Maybe used in the early phases of CRPS.

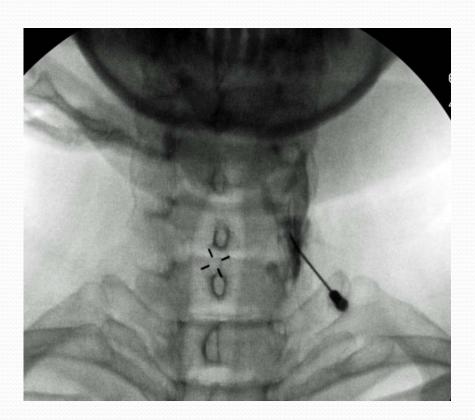
Recommend 2 times/ week for about 3 weeks.

Use of Exparel (long acting liposomal bupivacaine)

Strongly recommend physical therapy simultaneously

Stellate Ganglion Block





Lateral View A/P View

Lumbar Sympathetic plexus block

Usually between L2-L4

Done for lower extremity symptoms in early phase

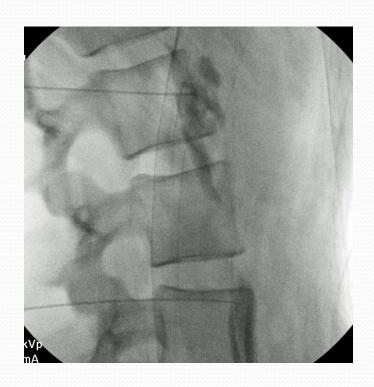
Be careful about possible trauma to exiting nerve roots

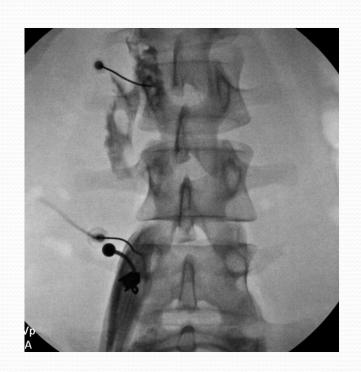
Recommend unilateral approach

Use of Exparel (Long acting liposomal bupivacaine is very helpful

Physical therapy to be done concurrently

Lumbar Sympathetic plexus block





Lateral View A/P View

Naltrexone:

- Pure mu receptor antagonist
- Has been around since 1980's
- Approved for opioid over dosage
- Now approved for alcohol and opioid addiction
- Available as Vivitrol. Depot injection of Naltrexone 380 mgs administered every 4 weeks
- Oral dose of Naltrexone (50mg tab) is about 100mgs/day
- Also as Contrave for weight loss(Long acting)

LOW DOSE NALTREXONE (LDN)

- Administered in small doses of 1.5mgs and titrated to 4.5mgs
- Compounded medication
- Works in the absence of opioids by temporarily blocking opioid receptors that then induce the brain to release endogenous endorphins.
- Acts to reverse central sensitization mediated via TLR-4 receptors
- Blocks the production of pro inflammatory cytokine. Glial cell inflammation is part of the etiology of central sensitization seen in CRPS.
- Increased endorphin production results in boost to the immune system documented by boost in T cell count by up to 300%. Auto immune issues are well documented in CRPS.

Our experience over 5 years

About 450 hundred patients

Conditions: CRPS, diabetic and peripheral neuropathy, fibromyalgia Post laminectomy pain syndrome, etc

Approximately 70% response rate.

Response seen in 1 week,1 month,3months.

Patients have been on opioids for longer than 25 years

Removed about 6-7 intrathecal pumps

No effect on liver/ renal function at low doses

Minimal side effects including headaches, gastritis, wakefulness, allergy

Can stop with out any side effects. Must stop before surgery Usually about 48hrs

Costs about \$15.00 per month

May need oral ketamine for breakthrough pain

Ketamine

- Anesthetic agent
- Has been around since 1960's
- Extensive experience
- Relatively safe as regards cardiac and respiratory safety
- Has many side effects. Most common:
 - Nausea/Vomiting
 - Hallucinations
 - Tachycardia/Hypertension
 - Salivation
 - Dizziness

- Use in treatment of CRPS since 1990
- ❖ Pioneer Grahme Correll in Australia
- First done in USA by Ron Hubbard
- ❖ Made popular in USA by Robert Schwarzman
- Can be done as inpatient/out patient basis
- * Ketamine coma. Not recommended. Not approved in USA
- ❖ Must be conducted under supervision of trained physician
- Mandatory minimum monitoring to be done during the infusion
 - ❖ BP/ Heart rate/Respiratory rate/Oxygen saturation/LOC

- Start with history and physical examination
- Use Budapest criteria to confirm the diagnosis
- ❖ No investigation will confirm the diagnosis
- Enquire about all the various medication/interventions done before possible ketamine infusion
- Mandatory evaluation by cardiologist and psychologist
- ❖ Presence of severe cardiac issue are reasons not to initiate treatment
- ❖ Presence of severe psychological issues including bipolar disorder is contraindication for ketamine infusion
- ❖ Perform blood tests including SMAC, LFT before starting infusion

Out patient set up:

- Need a quiet and darkened room
- May allow personal music but no video during infusions. Encourage attendants to leave the room
- Adequate monitoring
- Presence of resuscitation equipment
- Presence of nurse to monitor patient during the infusion
- Availability of physician at all times
- Record all parameters, before infusion and every hour after that
- All patients need to meet criteria for discharge before leaving infusion center

Our office protocol based on Correll/Schwartzman

- We recommend that patients wean from opioids before they start ketamine infusions. If not do so during infusions. Better response noted.
- Premedicated with lorazepam 1mg orally. twice daily. Helps to reduce hallucinations.
- Day of infusion: Needs to be NPO
- Get baseline vitals; Start IV access/access IV port
- Give clonidine o.img tab orally with small amount of water. Hold if BP is below 100mm systolic
- Give bolus of 2mgs midazolam IV before starting ketamine; recommend another dose of midazolam during infusion. Reduces hallucinations. Occasionally need an additional dose
- May need ondansetron 4mgs IV if nausea is a problem. May need a second dose
- Scopalamine patch to be started before infusion. Has been very effective for nausea/vomiting

Ketamine Out patient protocol

- 5 days followed by another 5 days. Monday to Friday
- 2 days in two weeks
- 2 days in one month
- 2 days in two months
- 2 days in three months
- Protocol starts at 80mgs/4hrs.Increased to 100/150/200mgs daily till end of protocol.
- Higher doses of ketamine maybe used based on clinical judgement
- Booster doses are based on recurrence of symptoms both for dosage of ketamine and duration of boosters.

Start ketamine infusion either as per protocol or predetermined dose from previous infusion/day

Lidocaine may be added to ketamine infusion. Acts on sodium channels

Magnesium acts as NMDA receptor antagonist.

IVIG has also been used with some success

Bisphosphonates have also been used. Results have been difficult to replicate

Addition of intravenous acetaminophen has been helpful in patients with severe swelling

Infusion rate adjusted to deliver ketamine over a duration of about 4 hours

Administer additional doses of midazolam in about 2 hrs., and ondansetron(prn)

Monitor and note vitals every hour

Ensure patient meets criteria for discharge and discharged with responsible adult.

Our experience over 7 years

Total Patients Treated: About 100 patients

Total Sessions: More than 2700 sessions

Demographics

• Female:Male 80:22

Mean Age: 47 years

Mean Weight: 168 lbs

- > Average dose of medication
- Ketamine: 300mg(Highest dose 600mgs)
- Lidocaine: 95mg (Highest dose 300mgs)
- Ondansetron: 2mg
- Midazolam: 4mg (Highest dose 6mgs)
- Acetaminophen: 45mg
- Magnesium 1000mgs
- Zoledronic acid 7omgs

Retrospective Data Analysis

- Side effects noted during infusions (# of yes responses/total)
 - Nausea: 19/39, 49%
 - Vomiting: 7/39, 18%
 - Headaches: 7/39, 18%
 - Hallucinations: 19/39, 49%
 - Palpitations: 3/39, 8%
 - Dizziness: 10/39, 26%

Retrospective Data Analysis (cont.)

- Side effects noted after infusions (# of yes responses/total)
 - Nausea: 24/39, 62%
 - Vomiting: 9/39, 23%
 - Insomnia: 6/39, 15%
 - Hallucinations: 4/39, 10%
 - Sleep walking:1/39, 3%
 - Decreased appetite: 9/39, 23%
 - PGIC 4.65

Ketamine Inpatient protocol

Significantly more complicated than out patient

More safety issues need to be considered

Usual protocol lasts about 5 days.

Start infusion at 10mgs/hr Titrate dose upwards as best tolerated.

Target dose of about 40mgs/hr

Patients are in ICU type settings and monitoring

Have foley catheter in place

Need to be treated like unconscious patients with all precautions

Daily monitoring of liver function

Physical Therapy

Essential for therapy of CRPS

Start early and continue for as long as needed

Multiple modalities are needed

Most important to maintain function and range of motion

Best served by physical therapist aware and trained in CRPS

Good pain control with adequate physical therapy can make a very big difference to outcome

Treatment of CRPS other options

- Spinal cord stimulation
 - Newer technology including high frequency stimulation, burst technology, DRG stimulation,
 - Intellis platform
- Intrathecal pump Various medications including opioids, clonidine, bupivacaine, ziconotide, baclofen

Thank You Samyadev Datta, MD, FRCA Center for Pain Management 201 488 7246 sdatta@centerforpain.net

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