Treating the whole person, optimizing wellness in CRPS

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Pradeep Chopra, MD

Assistant Professor (Clinical)

Brown Medical School

USA

Disclosure and disclaimer

- I have no actual or potential conflict of interest in relation to this presentation or program

- This presentation will discuss “off-label” uses of medications

- Discussions in this presentation are for a general information purposes only. Please discuss with your physician your own particular treatment. This presentation or discussion is NOT meant to take the place of your doctor.

Disclosure

- Pain Medicine specialist with a special interest in complex pains in adults and children

- Training and Fellowship, Harvard Medical school in Pain Medicine

- Assistant Professor (Clinical) – Brown Medical School, Rhode Island, USA

Grading of treatment

- Effective 
- Worth trying 
- Use caution 
- Science 

How do you know if you have CRPS?

Features of CRPS

- Look for the features of CRPS yourself. The diagnosis of CRPS depends on very specific criteria
- www.rsdsa.org is a good place to start with

- The symptoms of CRPS can mimic other nerve pain conditions and vice versa

Cause of CRPS

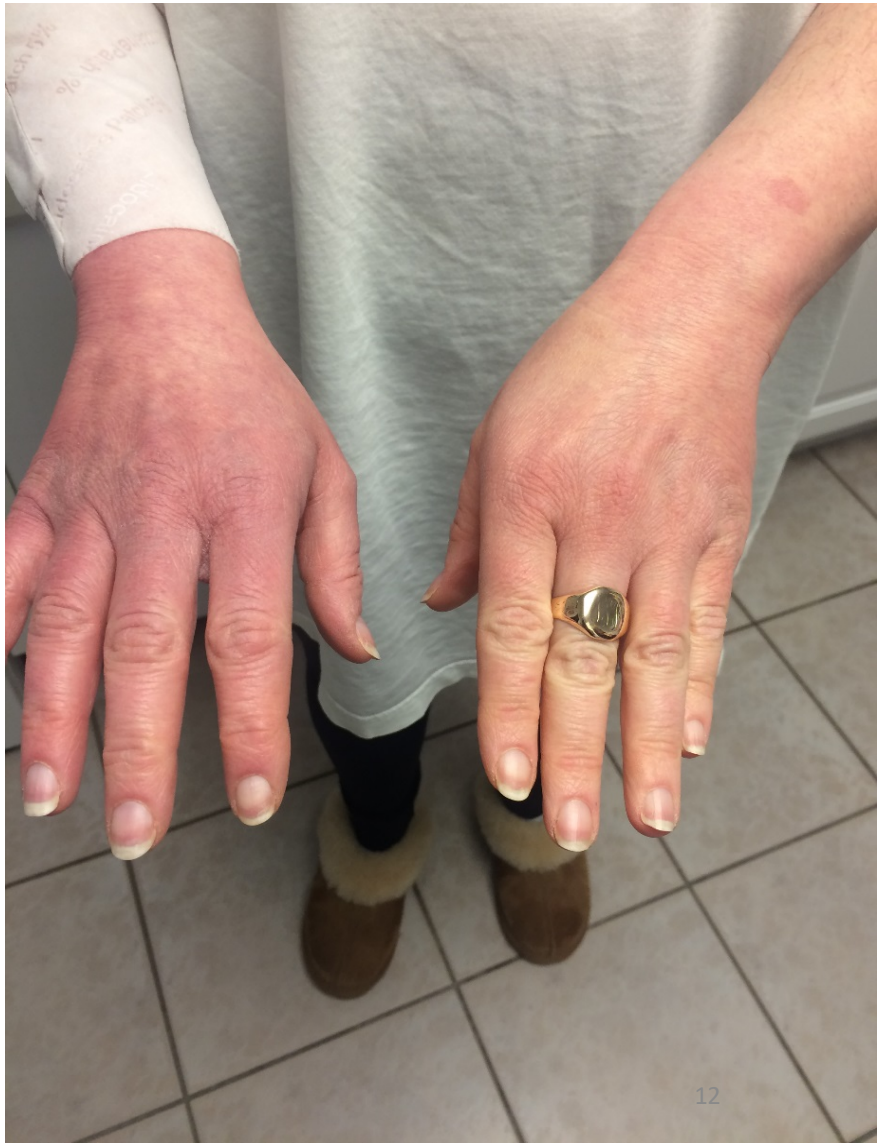
- Although by definition CRPS does not have a known cause
- Its just that we have not found the cause
- But what if we can identify a cause?
- Obviously, something is wrong
- Sometimes we can identify what is wrong and sometime we can’t

Diagnosis of CRPS

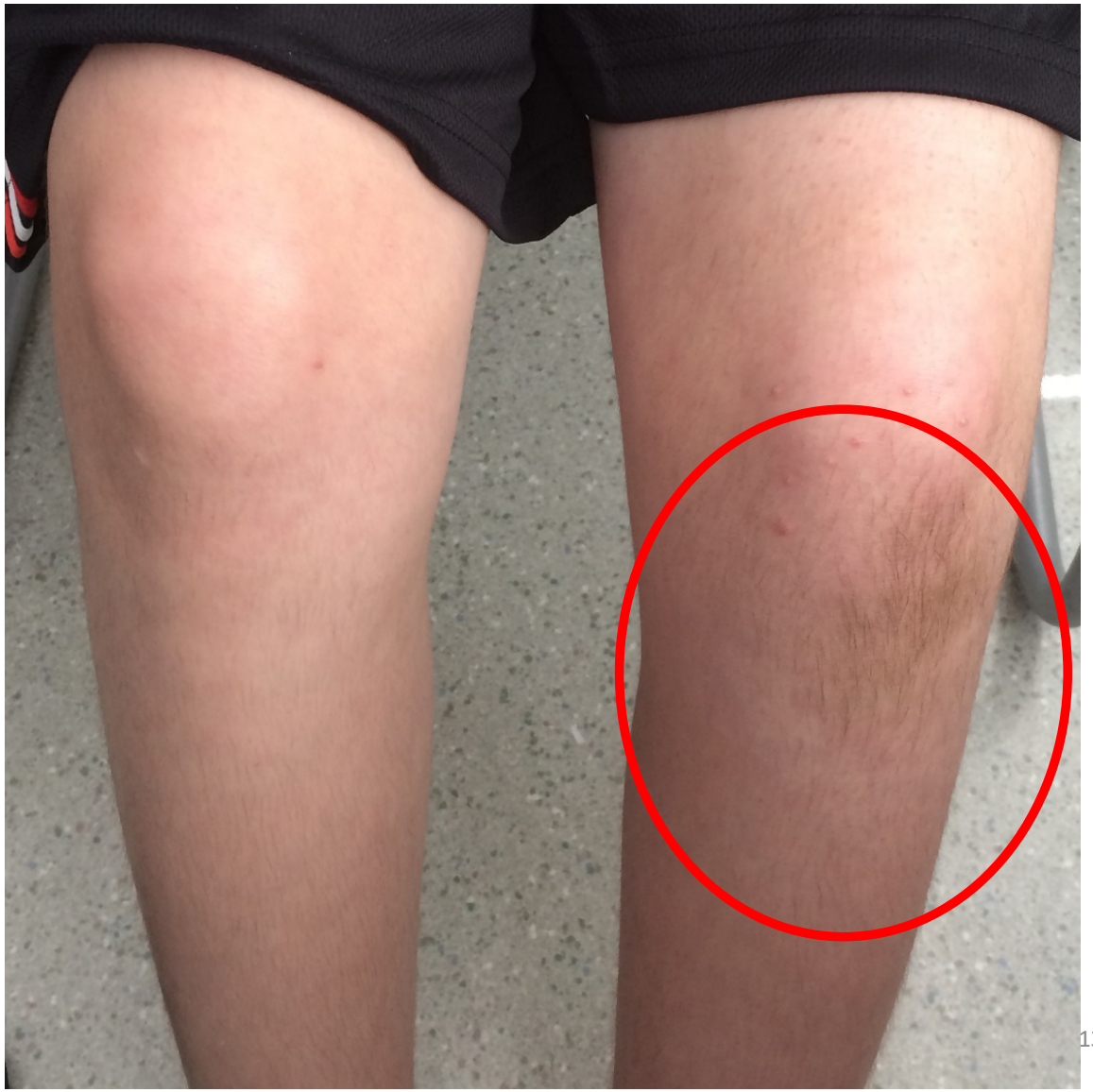
Signs and Symptoms of CRPS

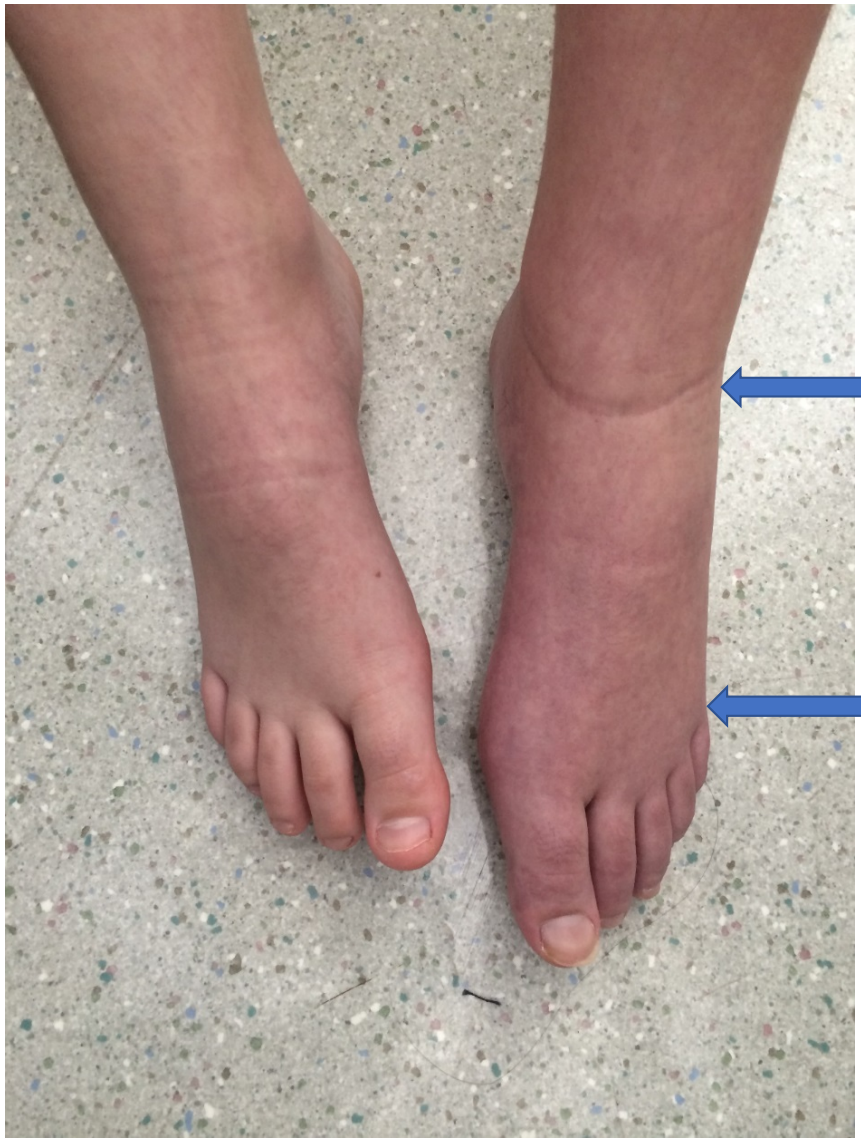
- Pain starts in one limb
- It can be affect any part of the body
- Constant pain, even at rest with intermittent exacerbations.
- Temperature difference between two sides
- Color difference – comes and goes
- Swelling – comes and goes
- Area of pain larger than the primary injury

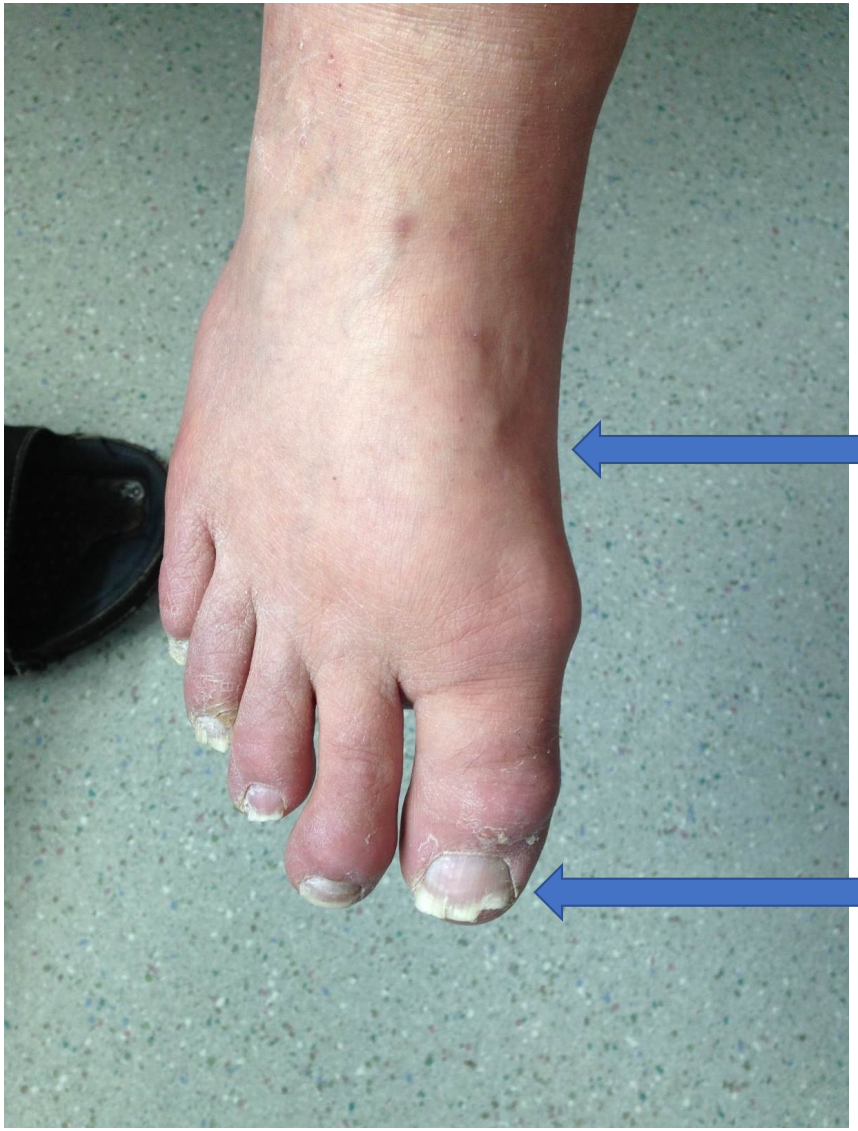
Color difference



Hair growth

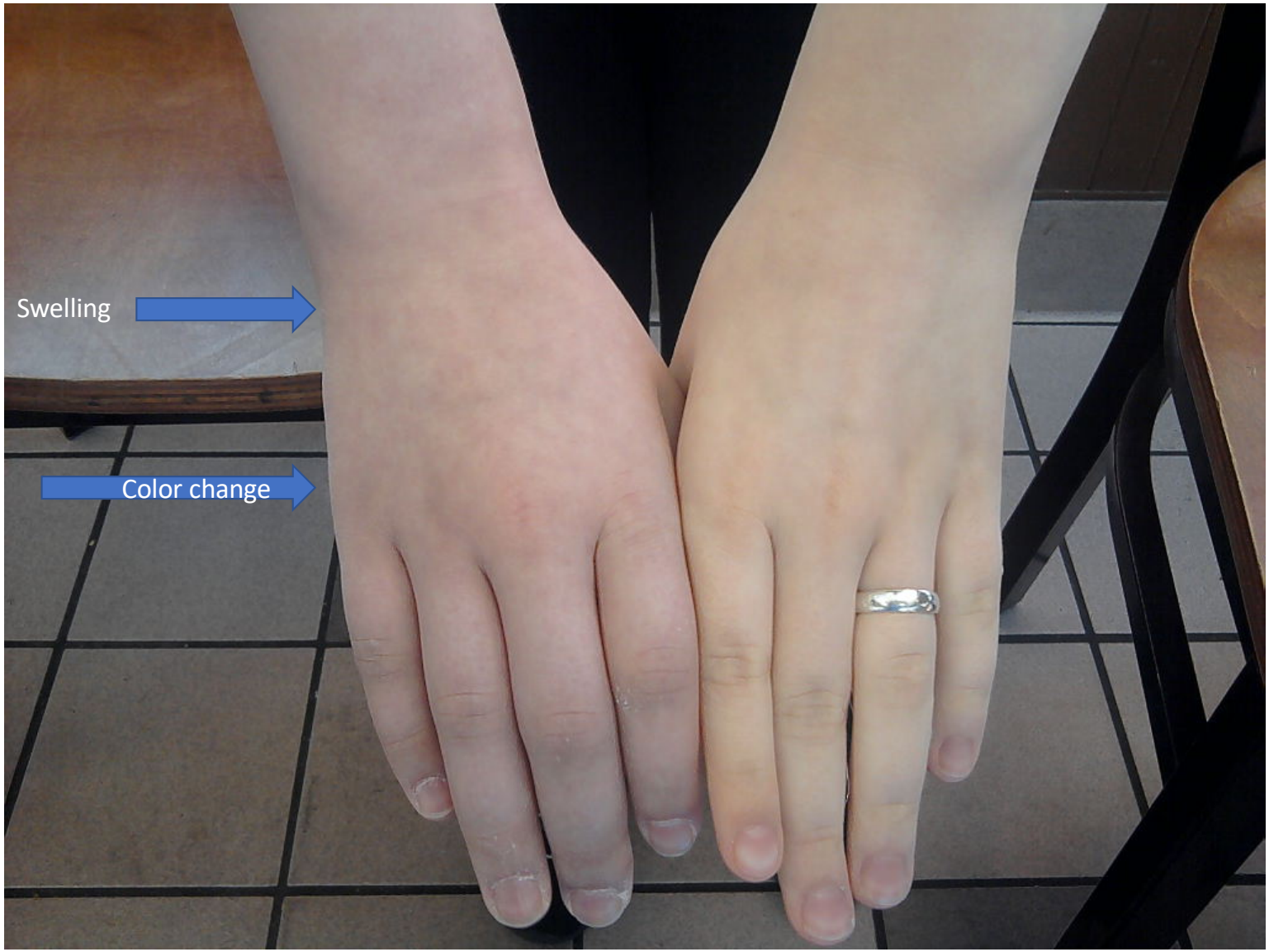



Swelling
Color change



Swelling

Nails growth faster, brittle, ridged


Swelling
Color change

Tests that are **not** helpful for diagnosing CRPS

- Imaging techniques – x-ray, MRI, fMRI, Three phase bone scan, bone density
- Blood tests
- Skin biopsy
- Nerve block - Sympathetic nerve tests – sweat test, sympathetic skin response,
- Nerve tests – EMG, nerve conduction,
- The tests MAYBE used if another diagnosis is suspected.

Atkins RM, Tindale W, Bickerstaff D, Kanis JA. Quantitative bone scintigraphy in reflex sympathetic dystrophy. Br J Rheumatol 1993;32(1):41-5.
Todorovic-Tirnanic M, Obradovic V, Han R, Goldner B, Stankovic D, Sekulic D, et al. Diagnostic approach to reflex sympathetic dystrophy after fracture: radiography or bone scintigraphy? Eur J Nucl Med

Best way to diagnose CRPS

- Thorough examination by a physician who is aware of the criteria for diagnosis of CRPS

Why is it so difficult to treat CRPS

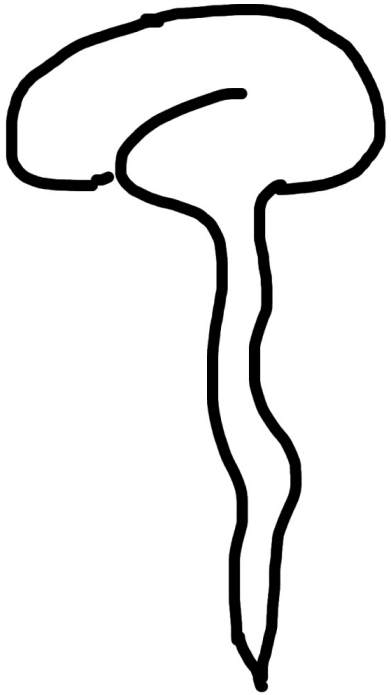
CENTRAL SENSITIZATION

Key concept to understanding CRPS

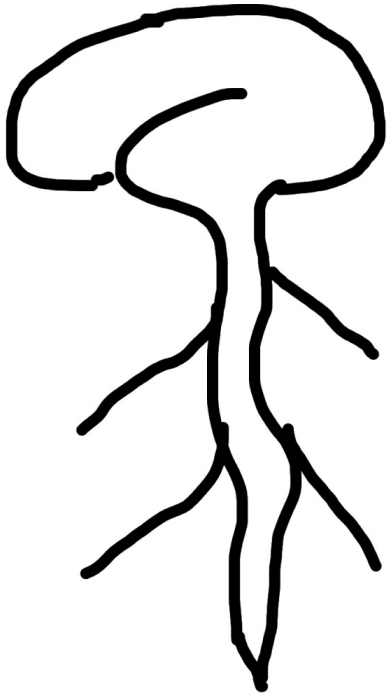
Central Sensitization

- The brain and spinal cord become sensitized
- A simple touch sensation becomes painful when it is perceived by the brain

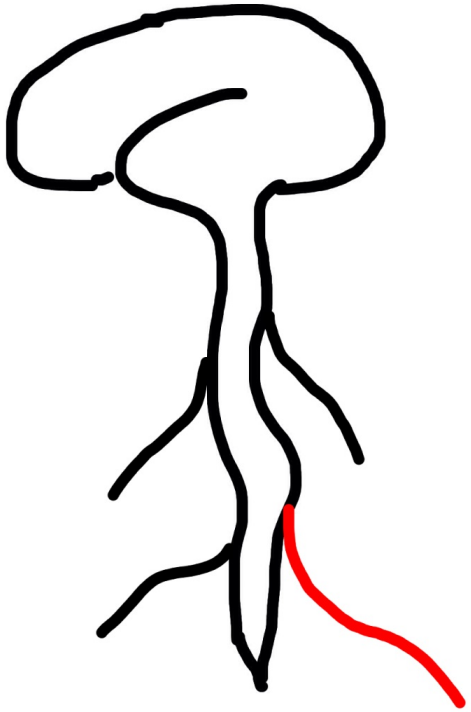
Brain and spinal cord



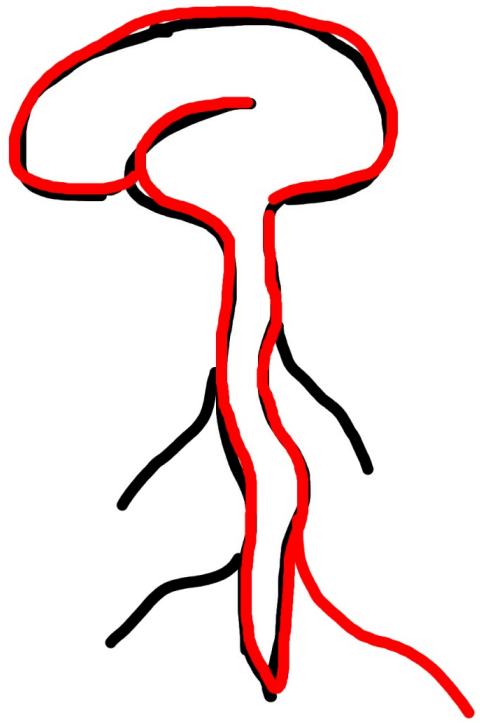
Brain, spinal cord, nerves



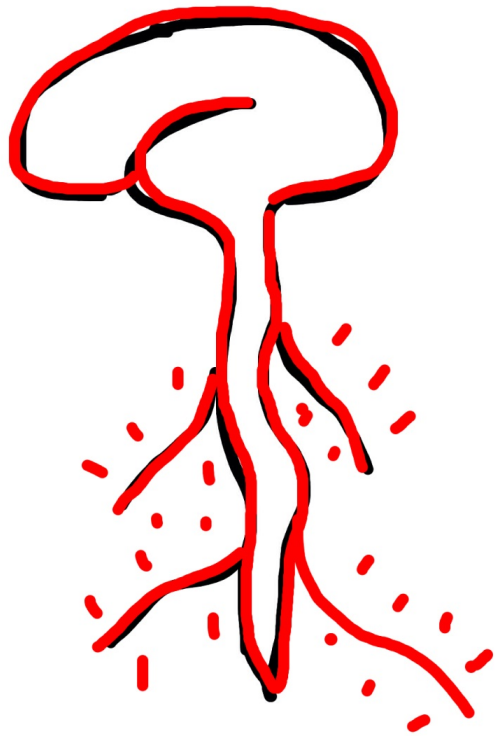
Painful nerve



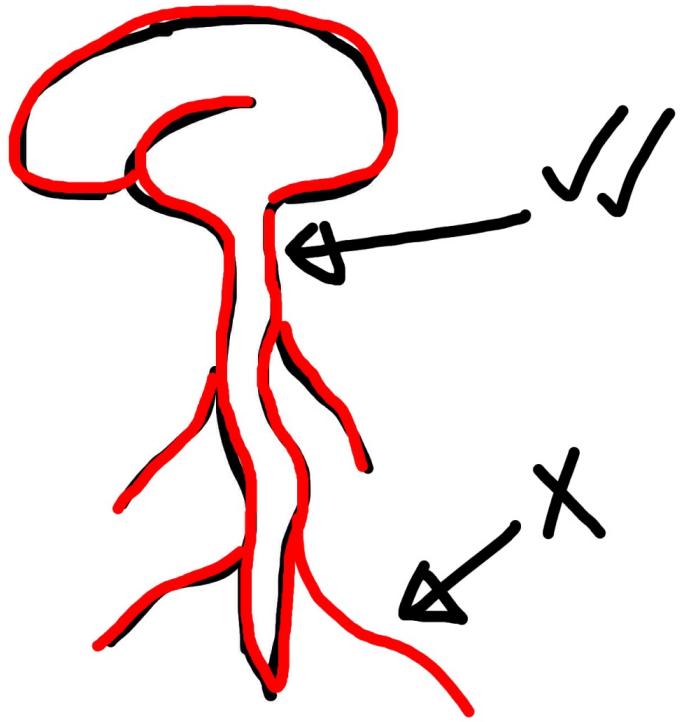
Brain, spinal cord sensitized – barrage of pain signals



Central Sensitization



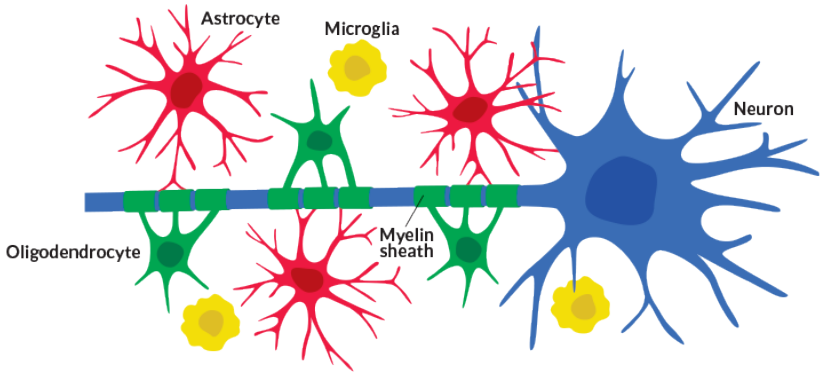
The problem lies in the brain and spinal cord, not the individual nerves



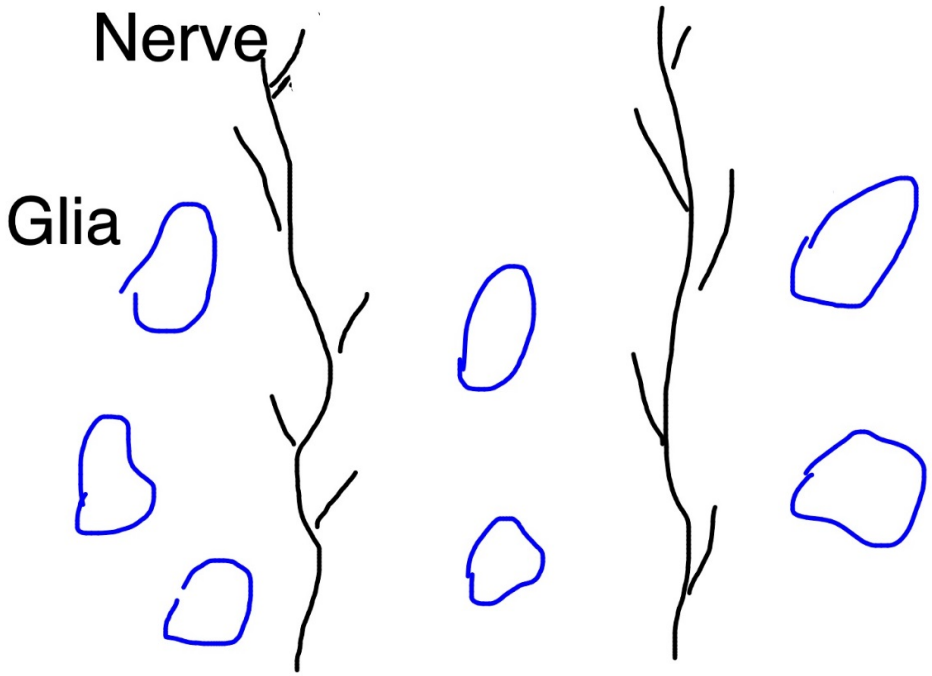
What really happens in CRPS /Central Sensitization

Central Sensitization: Activated Glial Cells

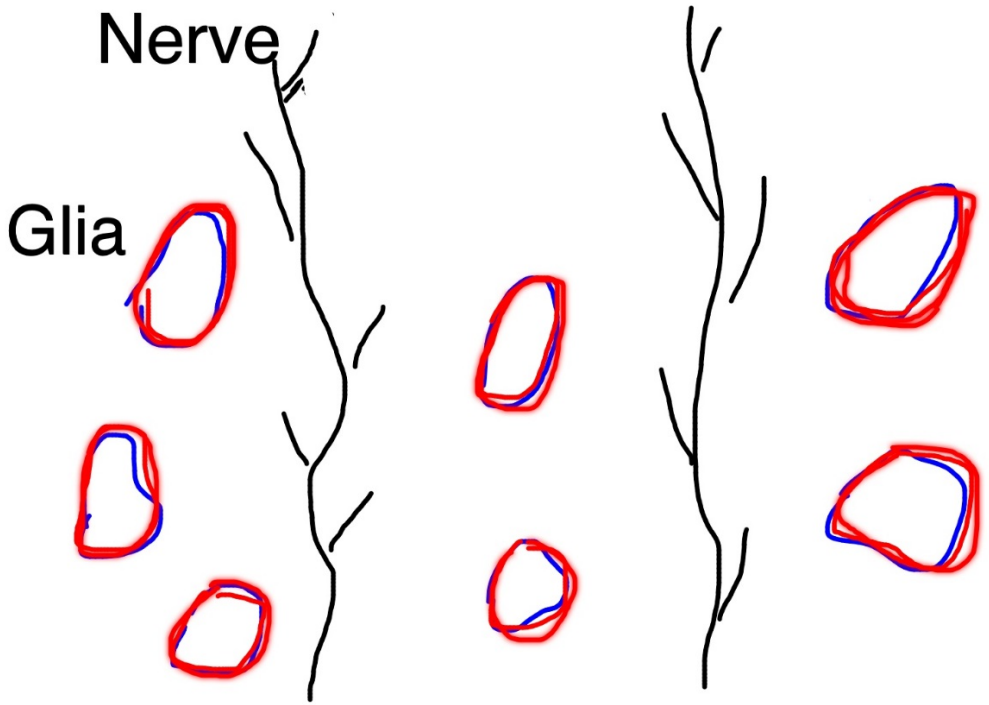
- Glial cells make up 70% of all the cells in our Central Nervous System
- Under normal circumstances, they remain dormant and are part of the nervous system's immune function



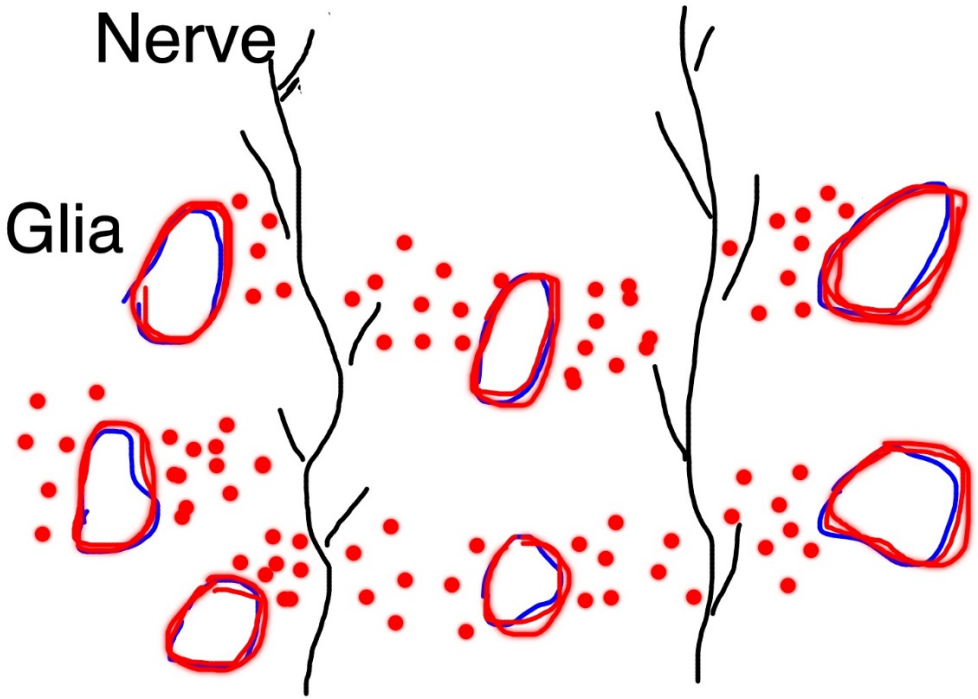
Glia and nerves under normal conditions



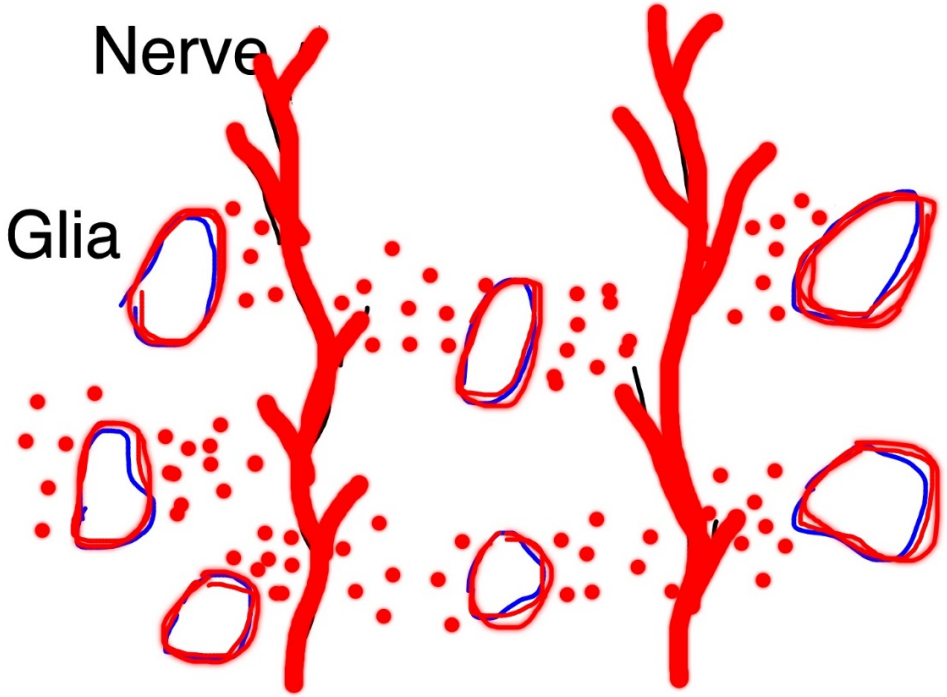
Activated Glia



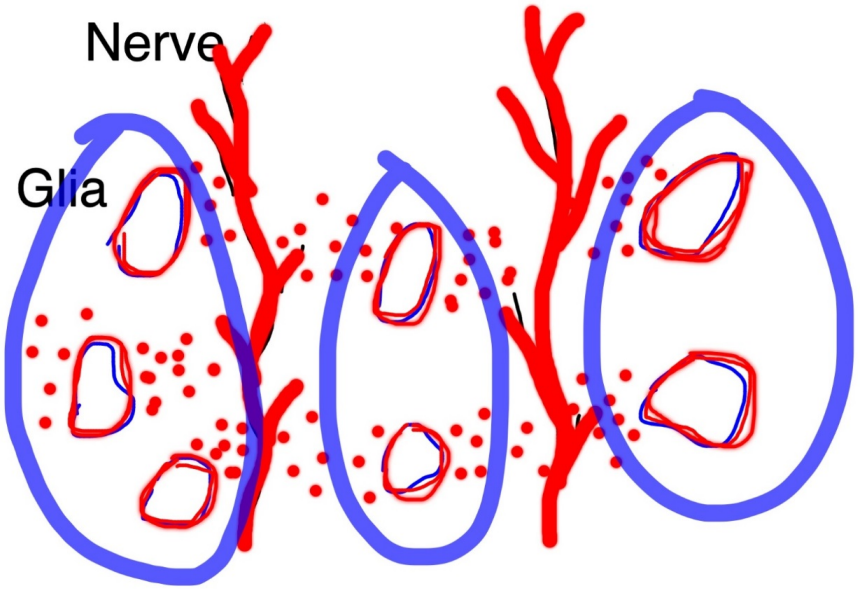
Fiery Chemicals released by activated Glia



Glial cells cause nerves to get inflamed



The problem is with the glia cells, not the nerves



Treat the inflammation

- Management of Complex Regional Pain Syndrome should be directed towards what's causing the nerves to become inflamed

- Treating just the nerves does not reduce inflammation of the nerves (that is why nerve blocks, spinal cord stimulators do not work).

Management

Complex Regional Pain Syndrome (CRPS)

Reflex Sympathetic Dystrophy (RSD)

Finding a doctor

- See a specialist who treats CRPS [not someone “its CRPS, I do not treat it” or “I do not know what it is, probably CRPS”]
- Make sure the doctor has a well rounded approach.
- Not someone who pushes spinal cord stimulators only or ketamine only or some expensive remedy
- Usually Pain Medicine specialists treat CRPS
- Look for an Anesthesia based specialist
- Must have a Fellowship training in Pain Medicine and be Board Certified in Pain Medicine

Finding a doctor

- There is a strong possibility that some cases of CRPS type I may be because of an autoimmune dysfunction.
- There has been a spike in autoimmune conditions in the last decade.
- Some patients respond well to autoimmune treatments.
- Remember, glial cells are part of the immune system.
- Consult an Immunologist

Management of CRPS – step A

- The first step to do is to confirm if it is CRPS.
- Very often patients are told that it is CRPS because a cause of the pain could not be found
- The criteria for diagnosis of CRPS very specific as discussed earlier

Management of CRPS – step B

- The next thing to do is to determine if it is CRPS I or CRPS II

CRPS I and CRPS II

- In CRPS I – we do not know the exact nerve that is damaged
- In CRPS II – limited to a specific nerve distribution
- Some of the treatments are common to both
- In CRPS II, fixing the cause of the nerve damage may help

Management of CRPS – possible causes of CRPS I

- Unknown
- Autoimmune dysfunction

CRPS II

This was the first CRPS discovered, even before CRPS I

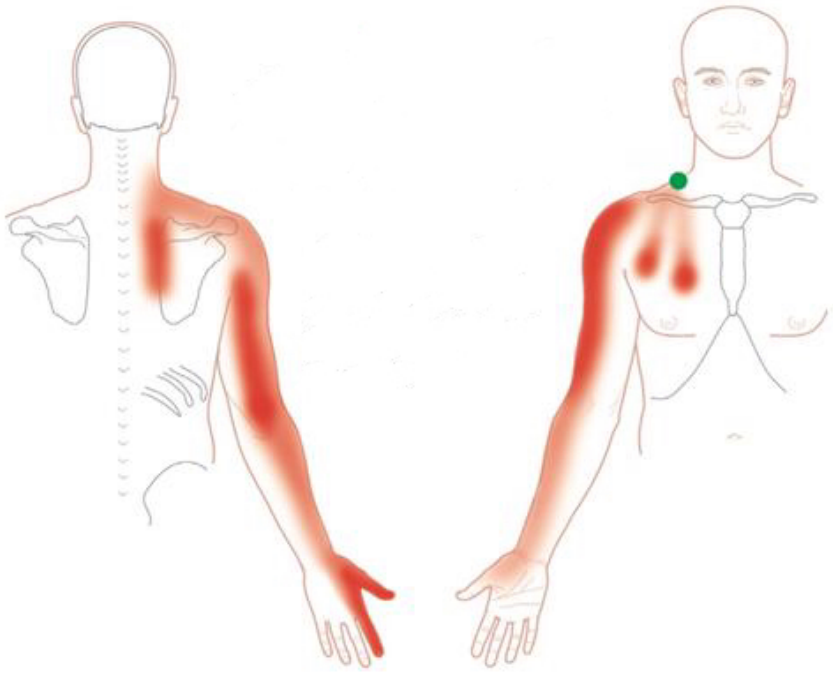
CRPS II

- Most of the symptoms are similar to CRPS I
- There is a major nerve damage that can be identified
- A careful examination may identify the nerve affected

Some examples of CRPS II

- Arms – Thoracic outlet syndrome, ulnar nerve entrapment
- Legs – Common Peroneal neuralgia, Tarsal Tunnel syndrome
- Scarring after a nerve injury.
- Joint Hypermobility (Ehlers Danlos Syndromes) – diffuse neuroinflammation from recurrent dislocations of joints

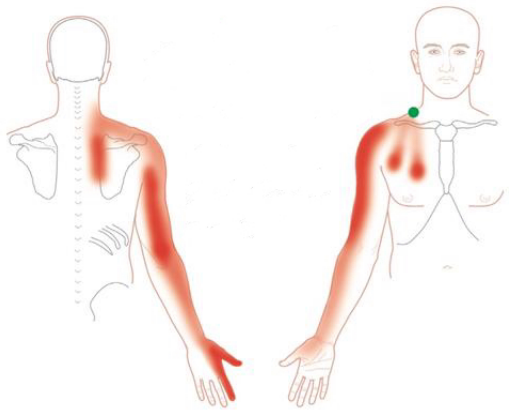
Pain patterns in Thoracic Outlet syndrome



Pain patterns in Thoracic Outlet syndrome

- CRPS type II as a result of compression of nerves to the arm.

- These patients may present with symptoms of CRPS



CRPS II from Thoracic Outlet Syndrome

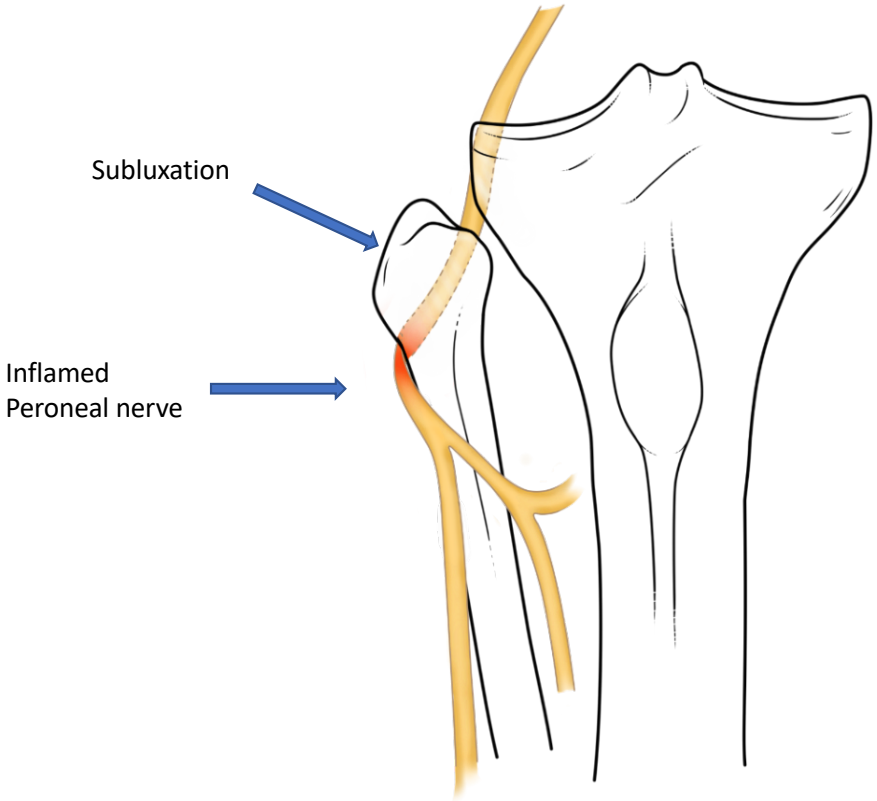
- Botox
- Surgical correction - if all else fails

An example of CRPS II in the leg

- Symptoms of CRPS II may develop in the leg after impingement of the Common Peroneal nerve (a nerve that goes down the leg)

- This nerve lives below and just outside the knee

CRPS II in the leg



Commonly used medications

- Gabapentin
- Pregabalin (Lyrica ™)
- Milnacipran (Savella™)
- Amitriptyline or nortriptyline
- Duloxetine (Cymbalta™) - avoid

Other commonly used pain medications

- Acetaminophen / paracetamol
- Non steroidal anti-inflammatory drugs (NSAID) like ibuprofen, naproxen
- Steroids
- Not very helpful in CRPS. They may help a little when taken with other medications

Low Dose Naltrexone (LDN)

Disease modifying agent for CRPS

Low Dose Naltrexone (LDN)

- Naltrexone has been FDA approved for 30 years.
- When taken in a small dose (Low Dose) it is disease modifying.
- It decreases glial cell activation
- LDN stabilizes the immune system

Low Dose Naltrexone (LDN)

- There are several theories as to how LDN may work.

1. Transiently blocks opioid receptor leading to positive feedback production of endorphins (Zagnon)
2. LDN increases production of OGF (opioid growth factor) as well as number of and density of OGF receptors by intermittently blocking the opiate receptor. Increased in OGF repairs tissue and healing.
3. Naltrexone blocks the effect of TLR4 (Toll Like receptors) which decreases glial cell activation

Low Dose Naltrexone (LDN)

- Dose can vary anywhere between 1.75mg to 4.5mg – ONCE A DAY
- May cause insomnia, mild headaches initially.
- Patients report increased physical activity, flare ups not as acute, better tolerance to pain.
- Recommend a trial of at least 6 months
- Inexpensive

J Neuroimmune Pharmacol (2013) 8:470–476
DOI 10.1007/s11481-013-9451-y

PERSPECTIVE

Treatment of Complex Regional Pain Syndrome (CRPS) Using Low Dose Naltrexone (LDN)

Pradeep Chopra · Mark S. Cooper

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Abstract Complex Regional Pain Syndrome (CRPS) is a neuropathic pain syndrome, which involves glial activation and central sensitization in the central nervous system. Here, we describe positive outcomes of two CRPS patients, after they were treated with low-dose naltrexone (a glial attenuator), in combination with other CRPS therapies. Prominent CRPS symptoms remitted in these two patients, including dystonic spasms and fixed dystonia (respectively), following treatment with low-dose naltrexone (LDN). LDN, which is known to antagonize the Toll-like Receptor 4 pathway and attenuate activated microglia, was utilized in these patients after conventional CRPS pharmacotherapy failed to suppress their recalcitrant CRPS symptoms.

Keywords Chronic pain · Complex regional pain syndrome · CRPS · Reflex sympathetic dystrophy · RSD · Neuropathic pain · Naltrexone · Fixed dystonia · Allodynia · Vasomotor · Ulceration · Dystonic spasms · Conversion disorder · Functional movement disorder · LDN

Introduction

Complex Regional Pain Syndrome (CRPS), formerly known as Reflex Sympathetic Dystrophy (RSD) is a neuroinflammatory condition that is characterized by a combination of sensory, autonomic, vasomotor, and motors dysfunctions. One of the characteristic symptoms of this condition is that the pain is out of proportion to the initial injury. Diagnoses of CRPS are often delayed because it is under recognized (Binkley 2012). If effective treatments are given early enough in progression of the disease, there is reduced chance for the spread of regional pain, autonomic dysfunction, motor changes, and negative sensory symptoms, such as hypoalgesia (Marinus et al. 2011). As CRPS progresses, it becomes refractory to sympathetic nerve blocks, conventional analgesics, anticonvulsants and antidepressants.

During neuroimmune activation, TLR4 (Toll-Like Receptor 4) is upregulated in microglia, resident immune cells of the central nervous system (Watkins et al. 2009). After transection of the L5 spinal nerve in the rat, TLR4 expression is increased in spinal microglia. This correlates with the rodent developing neuropathic pain (Tanga et al. 2005). From a post-mortem analysis of a CRPS patient, activated microglia and astroglia in the central nervous system (CNS) have been implicated in the generation of CRPS symptoms (Del Valle et al. 2009).

Activation of TLR4 in both microglia and CNS neurons augments the production of pro-inflammatory cytokines via the NF-κB pathway (Milligan and Watkins 2009; Leow-Dyke et al. 2012). NF-kB is a multi-functional transcription factor that is activated by c-Jun-N-terminal kinase (JNK), extracellular signal-related kinase (ERK), or p38 (Milligan and Watkins 2009). In activated glia and neurons, NF-κB activity promotes the production of pro-inflammatory cytokines and neurotoxic superoxides (Milligan and Watkins 2009; Leow-Dyke et al. 2012; Fellner et al. 2013), which

P. Chopra (✉)
Department of Medicine, Alpert Medical School of Brown University,
102 Smithfield Ave,
Pawtucket, RI 02860, USA

Low Dose Naltrexone (LDN)

- www.rsdsa.org

- LDN Research Trust
- https://www.ldnresearchtrust.org

- These websites has more information on LDN

CGRP (Calcitonin-related gene peptide)

- Nerve inflammation releases a chemical called CGRP
- CGRP causes increased blood flow, leakage of plasma around the nerve endings.
- This results in swelling, heat and redness.

CGRP antagonists - Disease modifying agent

- These drugs have been currently approved for treating migraines
- There are a lot of similarities between migraines and CRPS
- There is a possibility that CGRP antagonists may help CRPS pain,

- There are currently three CGRP blocking designer drugs in the market
  - Aimovig (erenumab-aooe)
  - Ajovy (fremanezumab)
  - Emgality (galcanezumab-gnlm)

Intravenous Immunoglobulin (IVIg)

- Patients develop auto-antibodies
- The auto-antibodies destroy their own tissue such as nerves
- IVIg is Infusion of good antibodies in patients with autoimmune conditions.

Ketamine

Central Sensitization

- Two things happen in Central Sensitization:
  1. Glial cells are activated
  2. NMDA receptors are activated

Central Sensitization

- Two things happen in Central Sensitization:
  1. Glial cells are activated
  2. NMDA receptors are activated

Central Sensitization - NMDA receptors

- In CRPS there is activation and proliferation of NMDA receptors

Activation of the NMDA receptors makes

1. Central Sensitization worse which increases CRPS pain and
2. decreases sensitivity to opioids

Milligan ED, Watkins LR (2009) Pathological and protective roles of glia in chronic pain. Nat Rev Neurosci 10:23–36

Ketamine is a good NMDA Receptor blocker

- One of the safest anesthetic drugs
- Powerful analgesic even at low doses
- Poor absorption when administered orally.
- Effective as IV or sublingual (Troche) or nasal

Correll GE, Maleki J, Gracely EJ, Muir JJ, Harbut RE. Subanesthestic ketamine infusion therapy: a retrospective analysis of a novel therapeutic approach to complex regional pain syndrome. Pain Medicine 2004;5(3):263-75.

Ketamine infusion – good news

- FDA is considering approving Ketamine infusions for the treatment of depression
- Once it gets approved, it should be covered by insurance
- More and more centers are now offering ketamine infusions

Factors that are important in getting the best out of a ketamine infusion

- Ketamine infusions are good only if done in conjunction with other therapies

Low dose Ketamine in CRPS

- Administered in low doses – ketamine blocks NMDA receptors without causing too many side effects
- In CRPS it decreases Central Sensitization
- Rough estimates – 85% show improvement in daily activities, reduction in their medications and improved lifestyles
- It is not a cure. It is to be done along with other therapies

Correll GE, Maleki J, Gracely EJ, Muir JJ, Harbut RE. Subanesthestic ketamine infusion therapy: a retrospective analysis of a novel therapeutic approach to complex regional pain syndrome. Pain Medicine 2004;5(3):263-75.

Ketamine – out patient

- Loading dose - ketamine over 10 days –Start at a low dose, increase as needed
- Infusion done over 4 to 5 hours
- Full standard monitoring
- Qualified personnel must be present at all times with the patient

IV Ketamine - boosters

- Very important part of the treatment protocol
- As the effect of the initial ketamine wears off, the glial cells begin to get activated again.
- Boosters for one day or two days every 4 to 8 weeks depending on the severity, chronicity and response
- The protocol has to be customized to each patient

Ketamine side effects

- Most of the side effects are temporary and short lived and reversible.
- We do not know of any long term side effects of ketamine infusions.
- Temporary side effects: Nausea, vomiting, colorful dreams, hallucinations, headache

Ketamine oral

- Oral ketamine – don’t bother
- Unpredictable effects

Ketamine for CRPS

- Trial of either ketamine nasal or under the tongue.
- If a person responds somewhat to Ketamine nasal or under the tongue, then
- It is worth moving forward with trying IV ketamine.
- Use ketamine nasal or under the tongue for flare ups only
- Alternate between using ketamine nasal and under the tongue every few months.
- Do not stay on either for prolonged periods of time.

Sensory Deprivation Therapy

- Isolation tank.
- Warm water with high quantities of EPSOM salt
- Subject floats on the water because of the high salt content
- No lights or sounds in the room
- All external stimulation to the Central Nervous system (brain and spinal cord) is cut off.
- Very helpful for Central Sensitization

Spinal Cord Stimulator (SCS)

- An electrode is inserted surgically into the epidural space and connected to an implanted generator
- The electrode produces an electrical current is felt as a tingling sensation and suppresses pain.
- Mechanism of action unknown
- Painful and expensive
- No great benefit after a few years
- Dorsal root ganglion stimulator – not helpful

Kemler MA, Barendse GA, Kleef M van, Vet HC de, Rijks CP, Furnee CA, et al. Spinal cord stimulation in patients with chronic reflex sympathetic dystrophy. N Engl J Med 2000;343(9):618-24.
Bennett DS, Alo KM, Oakley J, Feler CA. Spinal cord stimulation for complex regional pain syndrome I (RSD): a retrospective multicenter experience from 1995 to 1998 of 101 patients. Neuromodulation 1999;2:202-10.

Desensitization – Bad idea

- Rice bowl, rubbing with a piece of cloth, paraffin bath, etc.
- Desensitization exercises have been recommended for a long time for CRPS
- The idea of desensitization came from treating pain as a phobia
- Pain in CRPS is real pain, not a mental condition
- Worsens Central Sensitization, harmful for CRPS

Physical therapy modalities

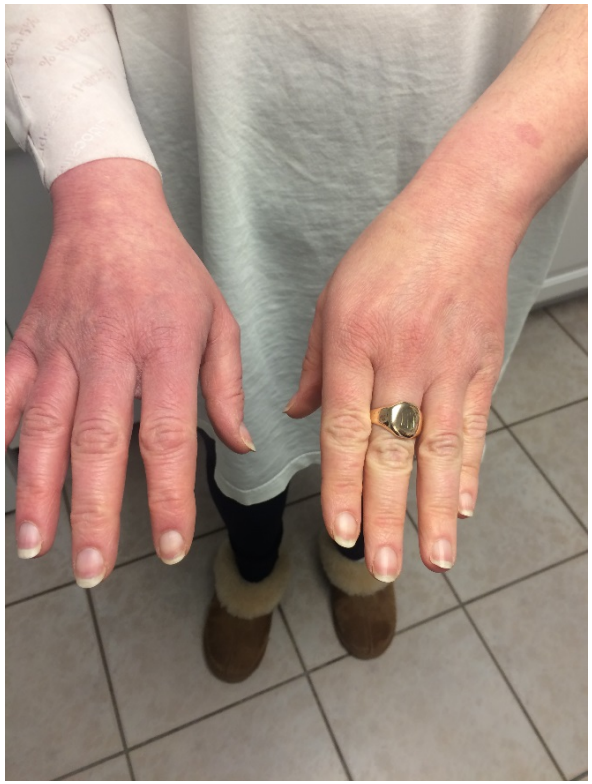
Physical movement

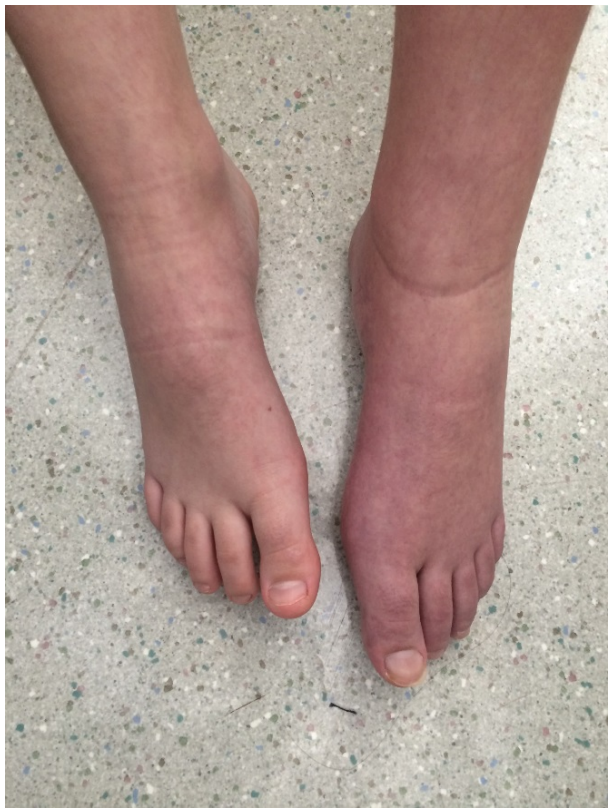
- Moving the limbs as much as possible is very important to prevent atrophy and contractures
- Physiotherapy does not have to be hard and difficult.
- It should be slow and paced.
- Its more important to be consistent every day.
- ”No pain, no gain” – does not apply here

Mental Health

- The cause of CRPS is NOT a psychiatric condition.
- It is definitely NOT in your head.
- Move away from providers who even suggest that
- CRPS, like all chronic conditions causes a feeling of despair and anxiety – reasonable to see a mental health provider for that

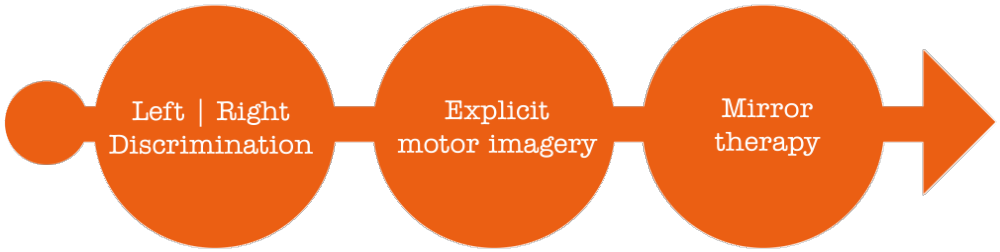
These are not manifestations of a psychological condition





Graded Motor Imagery

Graded Motor Imagery



- Left / right discrimination
- Explicit Motor imagery
- Mirror therapy
- www.gradedmotorimagery.com

Neridronate – not helpful

- Very similar to alendronate (Fosamax®), Pamidronate (Aredia®)
- Very small trial.
- Very select group of patients.
- Only patients who had bone changes were studied.
- Studies in UK were stopped
- First study in USA was not successful.

Varenna M, Adami S, Rossini M. Treatment of CRPS I with neridronate: a randomized, double blind, pacebo controlled study. Rheumatology. Doi 110.1093/rheumatology/kes312 274,299

Vitamin D

- Vitamin D promotes Calcium absorption in the gut
- Helps bone development
- Helps muscle and immune function
- Reduces inflammation

Antioxidants

Free Radical scavengers (Antioxidants)

- Alpha Lipoic Acid
- Vitamin C
- DMSO (Dimethyl sulphoxide) – cream or lotion
- N-Acetyl Cysteine (NAC)

- They are available over the counter

Alpha Lipoic acid (ALA) 1

- Free Radical scavenger
- Promising results in diabetic neuropathy and other polyneuropathies
- No trials in CRPS
- Has been approved in Germany for treating neuropathic pain

Kapoor S, Foot Ankle Spec, 2012 Aug;5(4); 228-9
Snedecor SJ, Sudarshan L, Cappelleru JC etc al. 2013 Pain Pract, Mar 28

Alpha Lipoic acid (ALA)

- Its also helps with autonomic neuropathy (common in CRPS) POTS
- Effective when taken as IV (Intravenous)
- May be taken orally
- Dose: 600mg to 1200mg per day
- Start low, go slow

Vitamin C

- Natural antioxidant
- There are several studies that have shown that Vitamin C can prevent CRPS after a fracture
- Vitamin C 500 mg was shown to prevent development of CRPS
- Vitamin C 500mg/day may help in patients who have developed CRPS
- No value to going higher than 500mg / day

Zollinger Paul, Tuinebereijer, Keir R, Breederveld, 1999, Lancet
Jae Hun Kim1, Yong Chul Kim2 *International Journal of Medical Sciences*
2017; 14(1): 97-101. doi: 10.7150/ijms.17681

N- Acetyl Cysteine (NAC)

- Useful for cold allodynia
- N-Acetylcysteine 600mg three times a day for three months
- Start low, go slow

Perez RS, Zuurmond WW, Bezemer PD, Kuik DJ, Loenen AC van, Lange JJ de, et al. The treatment of complex regional pain syndrome type I with free radical scavengers: a randomized controlled study. Pain 2003;102(3):297-307

Grading of treatment

- Effective
- Worth trying
- Use caution
- Science

Oxytocin

- Chemical produced naturally in the brain
- Taken as a nasal spray, under the tongue
- Especially helpful in flare ups (acute pain)
- Two mechanisms by which oxytocin reduces pain
  - Directly on the spinal cord to turn down pain signals
  - By releasing endorphins

Rash JA, et al Oytocin and Pain. Clin J Pain 2014;30-453-462

NC10 rule

Expectations from different therapies

Children and CRPS

- It's the exact same disease as in adults yet physicians in children's hospitals recommend intense physical therapy and psychiatric treatment as the main treatment.
- No pain treatment is offered

- If they fail to respond to physiotherapy, they are labelled as having a psychological problem – it's the child's fault

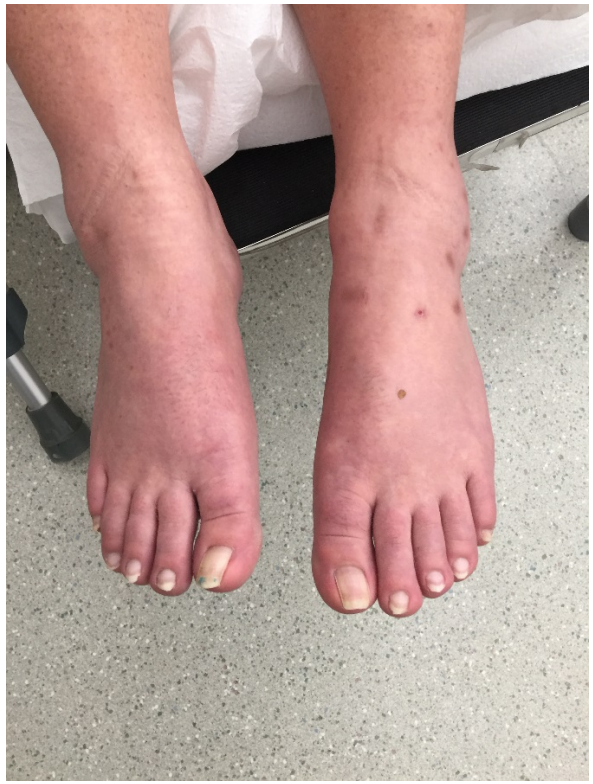
Children and CRPS

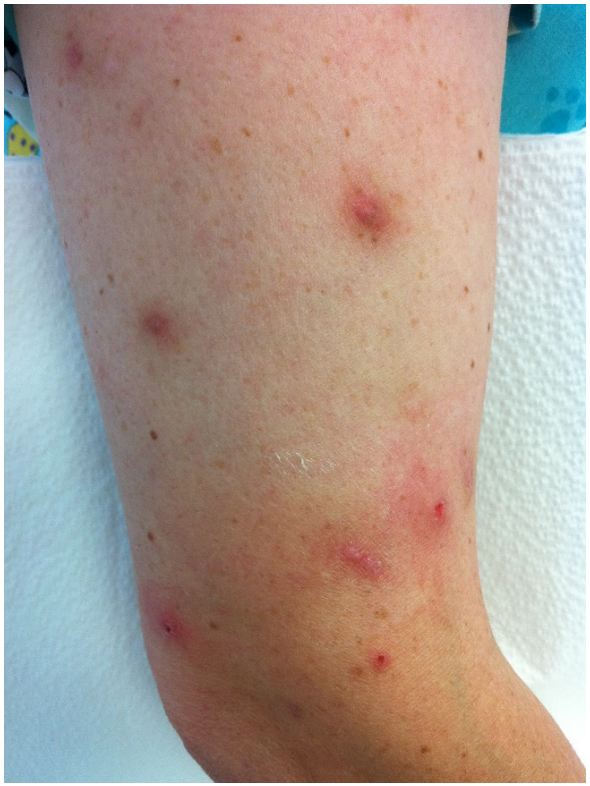
- It is often labeled as a behavioral disorder, Conversion Disorder
- Concerned Parents are labeled as having Munchausen's syndrome
- To make any of the above diagnosis is very challenging.
- Usually takes years by a Psychologist in conjunction with other treating physicians.
- Cannot be made by physicians with little or no mental health training

Children and RSD

- CRPS in children is often associated with other conditions such as
  - Ehlers Danlos Syndrome (EDS) – joint hypermobility
  - Mitochondrial disorder
  - Nerve entrapment

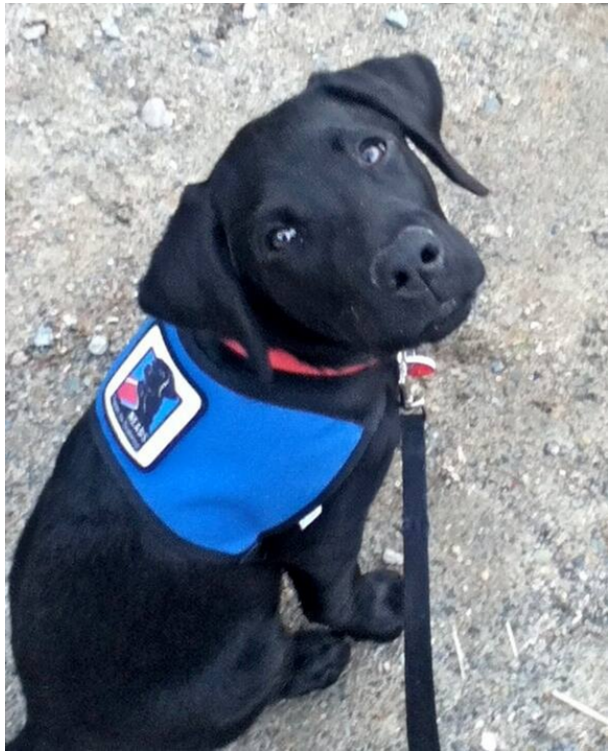
Skin Lesions in CRPS – use ketamine ointment





Service Dogs

- Help with functioning and independence
- Constant companion, will often sense its owners pain and will comfort them both physically and emotionally
- Can sense distress and call for help
- Service dogs give patients a feeling of security allowing them to be more active physically and socially



Pregnancy and CRPS

Pregnancy and CRPS - prenatal

- CRPS not known to affect fertility
- In most cases, CRPS pain gets much better during pregnancy
- Care should be at a high risk pregnancy center
- Discuss with Obstetrician and team about the issues with CRPS

Natural delivery or C-section?

CRPS and natural delivery

- Prolonged pushing
- Episiotomy incision
- Legs in stirrups
- There is a lot of touching, pushing and moving

CRPS and C-section

- Surgical incision
- No excessive pushing – causing tissue trauma
- No episiotomy

CRPS and delivery

- Discuss with Obstetrician about finding a middle ground – if no significant progress after pushing for a period of time, consider C-section
- Opt for epidural or spinal anesthesia, if possible.

Surgery and Complex Regional Pain Syndrome (CRPS)

Surgical trauma and Complex Regional Pain Syndrome (CRPS)

- Start gabapentin or pregabalin 2 weeks before the surgery
- Vitamin C 500 mg one daily. Start 7 days before surgery and continue for 45 days after surgery

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Surgical trauma and CRPS - Intra – operative

- Use intravenous ketamine as part of anesthesia
- Apply topical numbing medicine over IV site before insertion of needle
- IV must be inserted with minimum trauma (first shot, smallest needle possible)
- Epidural or spinal anesthesia, if lower body surgery
- Request that the chart be marked,

Hospital

- Ask for a sign over the bed that the affected limb is not to be touched.
- Avoid loud sounds, bright lights
- Cage over the affected limb
- Have a friend or family member to make sure that the area with CRPS is not touched

Palmitoyl ethanol amide (PEA)

PEA

- Now available in USA
- Comes as pills and ointment.
- Place powder from capsule under the tongue for the first 10 days.
- Ointment works well over small areas

Blood sugar

- Glucose dysmetabolism – diabetes or impaired glucose tolerance
- Even a mild abnormality in glucose metabolism is a risk for developing nerve pain

Thank you

Pradeep Chopra, MD
snapa102@gmail.com
Phone 401 729 4985