CRPS/RSD: Updates on treatment

Complex Regional Pain Syndrome or Reflex Sympathetic Dystrophy

Pradeep Chopra, MD
Assistant Professor (Clinical) Brown Medical School
Director, Pain Management Center, RI
Where is Rhode Island? – squished between MA and CT
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.
Introduction

• Training and Fellowship, Harvard Medical school

• Pain Medicine specialist

• Assistant Professor – Brown Medical School, Rhode Island
What really happens in RSD or CRPS
We will discuss

• The nervous system
• Central Nervous system
• Glial cells
• Central Sensitization
Nervous system

- Made up of 2 parts – Central nervous system and Peripheral nervous system

- Central Nervous System (CNS) – brain and spinal cord

- Peripheral Nervous System – all the other nerves in the body (limbs, trunk etc)
Peripheral Nervous system

• These nerves serve as a warning system; responding to damaging sensations (trauma, inflammation)

• Different types of nerves carry different sensations (pressure, heat, cold, touch)

• Carry pain sensation message to the spinal cord and brain (CNS).
Central Nervous System (CNS)

- CNS consist of the brain and spinal cord
- The cells in the CNS are made up of:
  - Neurons (nerve cells) 10%
  - Glia 90%
- Glia are immune cells that release certain inflammatory chemicals
- In RSD, glial cells get activated and release inflammatory chemicals
- Inflammatory chemicals released, cause inflammation of the nerves in the central nervous system.
Sensing pain is not simply a process of relaying a signal from the body to the brain. It’s a complex mechanism involving a dynamic, multi-pathway process resulting in pain modulation. Pain signals from the body are processed even before they reach the brain. Neuropathic pain or RSD: there is a dysfunction of this pain signal processing.
What happens in the Spinal Cord

• When the pain signal reaches the SC, a complex system is in place to send, modify or cancel the message to the brain

• In CRPS as a barrage of pain signals from the body reach the spinal cord a number of changes take place

• The Spinal Cord processes which signals to send ahead to the brain and which ones to block or modify.
The Brain

• The pain signals that make their way to parts of the brain where it now becomes a conscious and emotional experience.

• The brain responds to the strength, repetitiveness and duration of the pain signals.

• It responds by firing impulses that inhibit the pain signals
Central Sensitization

- As the spinal cord and brain is flooded with a barrage of pain signals, the nerves in these structures become hyper-sensitized

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

- Receptors in the body are like keyholes
- Central Sensitization causes activation of a certain receptor called NMDA receptor
- Activation of the NMDA receptors makes the Central Nervous system more responsive to pain signals and decreases sensitivity to opioids
- Drugs that block NMDA receptors are: ketamine, dextromethorphan, amantadine, methadone.
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.
- In CRPS with Central Sensitization, these glial cells are activated.
- Activated glia release certain chemicals that cause nerves to become inflamed.
- Glial cells are an important link between the nervous system and the immune system and inflammation and pain.
Central Sensitization: Glia

- Activated glial cells release chemicals (cytokines) that cause nerve inflammation
- Treatments used towards de-activating glia maybe useful for managing CRPS
- Treatments that we know of are: medications and exercise /Physical Therapy
- Opioids / narcotics increase glial cell activation
Common clinical features of RSD

• Continuous burning pain
• Pain disproportionate in intensity to the inciting event
• Pain to touch – Allodynia
• Deep pain in joints with touch or movement
• Pain not in any specific nerve distribution or even to the site of injury
• Swelling
• Increased / decreased sweating
Symptoms of CRPS / RSD

- Pain
- Temperature difference
- Hypersensitivity
- Tremor, Involuntary movements, muscle spasms, atrophy (weakening of the muscle)
- Increased sweating
- Color difference
- Bone thinning
- Swelling
- Hair and nail changes
Common clinical features of RSD

- Weakness
- Tremor
- Dystonia
- Symptoms of disturbed body perception
Guidelines

• No really good guidelines.

• The best guidelines are from the Trend Consortium, Netherlands

• www.trendconsortium.nl
Who is at risk?

- Caucasians
- Women four times more than men
- Hereditary: The presence of antigens HLA-DR2 and HLA-DQ1 is higher in patients with CRPS.
- Yes, children can develop CRPS.
How common is RSD?

• Not sure – because there are a lot of cases that are undiagnosed and over diagnosed.
• USA: no great studies but estimated to be 50,000 new cases per year
• New cases of Parkinson's every year: 60,000
• Netherlands (Population: 16 million) – 8000 new cases per year
• Population of California 38 million
• CRPS is not as rare as its made out to be
Tests that are **not** helpful for diagnosing RSD

- Imaging techniques – x-ray, MRI, fMRI, Three phase bone scan, bone density
- Blood tests
- Skin biopsy
- Sympathetic nerve tests – sweat test, sympathetic skin response,
- Nerve tests – EMG, nerve conduction,
- The tests MAYBE used if another diagnosis is suspected.
Management of CRPS / RSD
Basic guidelines in treating RSD

- Start treatment immediately, even if you suspect RSD
- Must be evaluated by a Pain Medicine specialist or a physician who is very familiar with it, to start appropriate therapy
- Treatment should be directed towards restoration of function
- Multidisciplinary approach - team work
- Physical Therapy must be gentle in the beginning and stay below pain threshold and not overly exacerbate pain
Glial cell attenuators

- Drugs that decrease glial cells activation are still in experimental stages, but there are some that are used clinically
- Minocycline – glial cell modulating, in animal experiments. It’s a tetracycline often prescribed for acne
- Propentofylline – Neuroprotective, glial cell modulating. Used for dogs at this time only. Under research
- Ibudiblast – Used for the last 20 years in Japan and Korea for asthma and stroke. Glial cell attenuator. Neuroprotective.
Opioids and CRPS and Glia

• Opioids taken chronically have been shown to increase glial cell activation

• Glia play a key role in developing tolerance to opioids.

• Increased tolerance to opioids leads to increasing the dose of opioids which, in turn, cause further glial cell activation

• Similarly, drugs that decrease glial cell activation also increase the effectiveness of opioids.
Low Dose Naltrexone (LDN)

• Naltrexone blocks the effect of opioids.
• Approved 30 years ago by the FDA for opioid and alcohol addiction
• In the late 1980’s it was discovered that at low doses it helped patients with immune disorders.
• Since then, LDN has been used extensively by patients with immune disorders like Multiple sclerosis, Crohn’s disease, Rheumatoid arthritis.
Low Dose Naltrexone (LDN)

- There are several theories as to how LDN may work.
- Low side effect profile
- Inexpensive
- Effective in CRPS
Severe RSD with skin ulceration
IV ketamine and LDN
Case of RSD treated with LDN

RSD with dystonia before LDN

RSD after LDN
Ketamine

• Approved by FDA in 1970 as an anesthetic. Not approved for its use in treating RSD

• One of the safest anesthetics in use – it does not lower blood pressure, does not slow breathing (unlike other anesthetics)

• World Health Organization classifies it as a core medicine in its ‘essential drugs list’

• Drugs that block NMDA receptors work well on nerve pain

• Side effects – nausea, dreams, hallucinations (in higher doses)
Ketamine in RSD

• Administered in sub-anesthetic doses – blocks NMDA receptors without causing too many side effects
• In RSD it decreases Central Sensitization
• Administration: IV (put it in a vein), oral, sublingual (under the tongue), nasal (squirt in nose)
• 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
Ketamine protocols in RSD

• Low dose protocol:
  • Loading dose: a low dose IV ketamine administered over a few hours (usually 4 hours). It is increased everyday over the next 10 days based on the response.
  • Booster dose: Low dose IV ketamine is repeated for 1 or 2 days after 2 weeks and then again at 4 weeks to 6 weeks tailored to patient’s response

• In patient protocol:
  • Usually used only for the loading dose. A continuous 24 hour infusion done over several days
  • Follow up booster infusions may be done as an outpatient procedure
Ketamine for RSD – other preparations

- Sub-lingual (under the tongue/inside the cheek): also called ketamine troche.
  - It takes about 15 minutes to dissolve.
  - Useful for acute flare ups
  - Can be titrated to effect (more or less depending on the pain)

Oral:
- Much higher doses need to be taken
- Unreliable absorption and effect

Ointment
- Useful in the very early stages only
- Helps with skin lesions
- Painful to apply
Nerve Blocks

- Sympathetic nerve blocks – Stellate ganglion blocks for arms, lumbar sympathetic blocks for legs.
- Risk of doing these procedures is very high
- Potential benefit is low
- No good studies to show that they work.
Spinal Cord Stimulator (SCS)

- An electrode (wire) is inserted surgically into the spine (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.
Spinal Cord Stimulator (SCS)

- 25% to 50% of patients develop complications requiring further surgery.
- Should be done in a very select group of patients, improves quality of life but not function
- In a huge study SCS reduced pain and improved quality of life but did not improve function for up to 2 years after implantation.
- From 3 years after implantation there was no difference between those who had it implanted and those who did not

Neuropathic pain medications

- Gabapentin (Neurontin®)
- Pregabalin (Lyrica®)
- Duloxetine (Cymbalta®)
- Milnacipran (Savella®)
Opioids / narcotics

- No long term studies
- Counterproductive for CRPS
- Activate glia through a receptor that is distinct from classical opioid receptors.
- Opioid induced activation of glia induces them to release neuroexcitatory pro-inflammatory cytokines, suppressing opioid analgesia
Exercise and Physical Therapy
Effect of RSD on function

• Pain decreases mobility of the limbs. They experience extreme pain with the slightest activity

• Not using the limb causes the muscles to atrophy (weaken) and the joints to become stiff

• Immobilizing a limb increases RSD pain
Physical Therapy - Goals

• Restore function

• Learn how to properly adjust limb movements
Physical Therapy - two types

- Patients who have recently developed RSD – PT should focus more on pain

- Patients who have had RSD for a while (Chronic) – PT should be more time based
Physical Therapy – Pain focused

- Preferred in recent onset RSD but can be used in chronic RSD
- The level and progression of exercise is determined by the intensity of the pain.
- The intensity of the exercise should be low in cases of (or days of) highly intense pain.
- Similarly, the intensity of exercise should be high if the pain is relatively low.
- Its not harmful if there is an increase in pain for a short duration (approx. 1 to 2 hours) after exercise
Physical Therapy – Pain Focused

• A program is designed based on the patients limitations

• Patient exercise within those limits.

• It builds confidence and increases confidence in using their limbs

• Pain focused PT has been shown to decrease considerably symptoms of recent onset RSD
Physical Therapy – Time focused

• The level of exercise is built over time unrelated to intensity of pain

• Preferred approach in cases of long standing RSD

• Pain focused PT can give way to time focused PT and vice versa
Other Therapies: Medications
PEA

• Palmitoylethanolamide (PEA)
• Endogenous lipid (produced in the body)
• Available in Europe
• Very good studies to show its usefulness in managing neuropathic pain
• No studies done for RSD
• Marketed as Normast and PeaPure
Bisphosphonates

• Group of drugs to treat osteoporosis

• Members: Pamidornate, alendronate, clodronate

• Some good studies using alendronate and clodronate to show helpful in treating RSD
DMSO (Dimethyl sulphoxide)

• Free radical scavenger
• Topical cream
• DMSO 50% cream has been shown to have a significant response in RSD
• Apply to the affected site five times a day
• Better effects in warm RSD
NAC (N-Acetylcysteine)

- Antioxidant
- Taken as a pill
- NAC was found to have a significantly better effect on cold RSD than DMSO cream
- Commonly used drug for cough, acetaminophen overdose.
Vitamin C

• Natural antioxidant
• Unclear as to how it helps CRPS
• There are several studies that have shown that Vitamin C can prevent CRPS after a fracture
• Recommended daily allowance of Vitamin C is 60mg (National Research Council, USA).
• Vitamin C 500 mg for 45 days to 50 days was shown to prevent development of CRPS
• ? Any value to using it in established CRPS, certainly helpful in prevention
Muscle Relaxants

- Cyclobenzaprine, tizanidine
- Not very helpful for muscle symptoms of RSD
- Baclofen and diazepam or clonazepam may have some benefit
- Intrathecal (spinal pump) baclofen is not helpful
Neurotropin®

- Non-protein extract from rabbits
- Exact mechanism not known
- Widely used in Japan to treat Neuropathic pain
- 24 Clinical studies conducted in Japan found an approximately 40% to 50% response
- Helps with allodynia (pain to touch) and hyperalgesia
Service Dogs

- Trained to each person’s physical impairments
- 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
- Provide stability while walking, open and close doors, switch on and off lights
Surgery and Acute trauma in RSD
Surgical trauma and RSD - Pre – operative

• Avoid surgery unless you have to
• Start gabapentin or pregabalin 2 weeks before
• Minocycline 1 day before and continue for 2 weeks after
• Vitamin C 500 mg one daily. Start day before surgery and continue for 45 days after surgery
Surgical trauma and RSD - Intra – operative

- Use intravenous ketamine as part of anesthesia
- Apply Synera® patch or some numbing medicine patch over IV site before insertion of needle
- IV must be inserted with minimum trauma (first shot)
- Epidural or spinal anesthesia, if lower body surgery
- Request that the chart be marked, label area with RSD that it should be handled with extreme care
Surgical trauma and RSD - Post – operative

- Continue low dose IV ketamine in the recovery room for a few hours – very important
- Continue, minocycline, gabapentin/pregabalin, vitamin C
- Continue epidural anesthesia for pain control, if inserted pre op, for at least 24 hours
Needle stick injuries

- Avoid needle stick injuries as far as possible – combine a blood test from different physicians into one procedure.
- Ask that the thinnest needle possible be used.
- Use a topical numbing cream (EMLA® or Synera® patch).
- Let them know that the veins are ‘difficult’. CRPS patients have thin and friable veins.
- Ask for the most experienced person to insert IV or blood draw.
- For those undergoing regular infusions (IV fluid rehydration or IV Ketamine) should consider a chest port.
- PICC line is not a good option.
RSD in children
Children and RSD

- Children develop the same symptoms

- 58% to 93% of cases of RSD in children will resolve with proper treatment

- Relapses following apparent healing are often observed (10% to 48%)

- More common in girls
Children and RSD

- It is often labeled as a behavioral disorder, conversion disorder and 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.
- Imperative that all other medical conditions have been ruled out.
- Cannot be made by physicians with little or no mental health training.
- Very important that parents pay close attention to the child’s complaints.
Children and RSD

• The incidence of these disorders (Munchausen's, Factitious disorder) is less than 1% far less than the incidence of CRPS

• There are no studies to show that it exists. Only 2 cases have been reported

• Parents should consult a physician familiar with CRPS because being labeled as one of the above is far more devastating and closes the doors to any further treatment for RSD
Children and RSD

- Often associated with other conditions such as
  - Ehlers Danlos Syndrome (EDS)
  - Mitochondrial disorder
  - Nerve entrapment
Ehlers Danlos Syndrome

- Defect in tissue (connective tissue) that provides support to many body parts
- Extremely loose joints (Double jointed)
- Dislocate or subluxate joints easily
- Hyperelastic skin that bruises easily
- Inherited
- Symptoms of CRPS may be either because of repetitive trauma or nerve damage
Mitochondrial Disease: Power house of the body

- Mitochondria are tiny organs found in cells of the human body
- They produce 90% of the energy for the body
- Mitochondrial disease is a genetic disorder where the mitochondria fail to produce enough energy
- Nerve cells require a tremendous amount of energy to function and these patients may present with symptoms of CRPS, or
- if they develop CRPS then its important to treat the mitochondrial disease first.
Nerve entrapment

- Often seen after a cast is put on

- Maybe cause pain either right away or after some time with chronic pressure over the nerve
Complications of CRPS
Complications of CRPS

- Can affect any organ
- Poor processing on working memory, language, executive function
- Lethargy, tiredness, weakness
- Syncope – dizziness and fainting
- Postural Orthostatic Tachycardia Syndrome (POTS) or Dysautonomia
- Chest wall pain due to dystonia
- Edema – neurogenic or inflammatory
Complications of CRPS

• Muscles – weakness (70%), atrophy, dystonia, spasms
• Bone and joint pain – very common, bone loss leading to fractures,
• Low serum cortisol levels (impaired hypothalamo-pituitary-adrenal function – low production of cortisol by the body). Maybe due to opioids
• Low thyroid function (hypothyroid)
• Skin changes
• Nails – brittle, ridging, thinning, grow faster or slower
• Hair – grows faster, thicker, curly and darker
Complications of CRPS

- Increased sweating (30%)
- Unexplained spontaneous bruising (Gardner Diamond Syndrome). May not be in an area that has been traumatized
- Bladder (25%) – frequency, urgency, urinary incontinence
- Gastrointestinal (41%) – Nausea, vomiting, intermittent diarrhea, Irritable bowel syndrome, dysphagia (food stuck in the throat)
- Gastroparesis – major issue in CRPS for more than 5 years. Slowing down of the intestines. Fullness with a little food, bloating. Opioids make it worse
Complications of CRPS / RSD: POTS

- Dizziness, fainting spells, heart palpitations
- POTS (Postural Orthostatic Tachycardia Syndrome) or Dysautonomia
- Patients have difficulty maintaining their blood pressure and heart rate with changes in position
- See a Cardiologist
- May confirm with a Tilt Table Test
Skin Lesions in RSD

- Often go undiagnosed. Little information on skin lesions
- Different types of skin lesions.
- Swelling and repeated episodes of cellulitis
- Bullae or raised skin lesions filled with fluid
- Early phase of CRPS – mottled red and sweaty
- Later phase of CRPS – smooth, cool, dry and thin
Skin Lesions in RSD

- May develop from tiny pinhead size to large areas of skin erosion
- Topical ketamine may be effective.
Summary

- CRPS is a chronic neuropathic pain
- It starts in the periphery (limbs or other body parts)
- Rapidly moves to the Central Nervous System causing Central Sensitization
- Diagnosed by clinical and physical examination
- No tests to diagnose CRPS
- Rapid fire pain signals from the periphery to the CNS causes the CNS to become hypersensitized – Central Sensitization
Summary

• Central Sensitization is a process in which the glial cells are activated.
• Activated glial cells release chemicals that cause nerve inflammation in the CNS
• Drugs and exercise help de-activate glial cells
• Start treating immediately, even if you suspect RSD
• Pain Medicine specialist or a physician very familiar with RSD
• Physical Therapist should be familiar with RSD
• Multidisciplinary approach works best
Summary

- Drugs that may help with deactivating glial cells – minocycline, ibudiblast, LDN
- Avoid opioids – activate glial cells, hypersensitize to pain
- Low Dose Naltrexone – good choice
- Low dose IV ketamine infusion – good choice
- Nerve blocks – not good literature to support its use
Summary

• Physical Therapy and exercise – very important. Aerobic functioning and weight loading

• PT – pain focused for initial cases and time focused for chronic cases.

• Other – PEA (Normast, PeaPure), Biphosphanates, DMSO, NAC, Neurotropin,

• Vitamin C

• Trauma or surgery – follow measure to prevent exacerbation or spread
Summary: Pediatric patients

- Children do better than adults
- A high percentage will resolve
- Not a behavioral condition
- Often mislabeled as conversion disorder, factitious disorder or Munchausen syndrome
- Rule out other conditions such as Ehlers Danlos Syndrome, Mitochondrial disorder, nerve entrapment
Acknowledgments

• All my wonderful and courageous patients
• Jim Broatch, Executive Vice President and Director, RSDSA
• Mark Cooper, Ph.D, Associate Professor, Department of Biology, University of Washington, Seattle
• Mothers with CRPS who never stop and mothers of children with CRPS who never stop