Complex Regional Pain Syndrome: Thoughts & Progress

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Off-label use of drugs will be discussed
CHRONIC POST-SURGICAL PAIN
RADICULOPATHY
PSYCHOLOGY
FIBROMYALGIA
NEUROPATHIC
ACUPUNCTURE
AUTOIMMUNITY
ALLODYNIA
QUALITY OF LIFE
MECHANISMS
INFLAMMATION
LOW BACK PAIN
MULTIDISCIPLINARY
IMAGING
NERVE BLOCK
PHYSICAL THERAPY
OPIONDS
PAIN
NSAIDS
SURGERY
100 MILLION AMERICANS
COSTS $635 BILLION
But what is PAIN?
When is acute pain no longer acute pain?
It's all about trajectory

Patients should be improving, not worsening, in the weeks after injury/surgery/trauma
Not all chronic post-injury pain is the same.

28 year old female
Twisted ankle
Persistent pain, swelling, redness, warmth of right foot
Complex Regional Pain Syndrome (CRPS)
A form of chronic pain affecting the limbs often resulting from minor trauma or surgery

- **Sensory**
  - Pain

- **Sudomotor**
  - Edema
  - Sweating
  - Hair or nail growth changes

- **Vasomotor**
  - Temperature changes
  - Color change

- **Motor**
  - Loss of ROM
  - Tremor
  - Weakness

Based on the Budapest Diagnostic Criteria (Harden et al. 2010)
CRPS Distinction Based on Etiology

Type I: No “major” nerve lesion

Type II: Detectable nerve injury
A Disease Spectrum for Peripheral Pain

Neuropathic Pain
Pain in the distribution of a peripheral nerve

CRPS Type I
Pain in a limb, not necessarily restricted to a dermatome
Additional features of CRPS

CRPS Type II
Pain in the distribution of a peripheral nerve
Additional features of CRPS

Erythromelalgia
Pain in a limb, usually not restricted to a dermatomes
Primary symptom is burning pain relieved by cooling
CRPS consists of two phases

**Acute/Peripheral**
- Warm limb
- Edema
- Elevated skin cytokines
- More responsive to treatment

**Chronic/Central**
- Cool limb
- Atrophy
- Elevated CNS cytokines
- Refractory to treatment
Isn't it normal to have post-injury inflammation?

Four classical signs of inflammation described by Celsus (circa 30 BC-30 AD)

Clinical considerations for CRPS

5-26 cases per 100,000 per year

50,000 new cases per year

Underrecognized?
Underdiagnosed?

Risk factors for the development of CRPS

- Female gender (3:1)
- History of trauma or surgery
- Genetics
- Cast “tightness” after injury
What is up with cast “tightness”?

Effect of vitamin C on frequency of reflex sympathetic dystrophy in wrist fractures: a randomised trial

Paul E Zollinger, Wim E Tuinebreijer, Robert W Kreis, Roelf S Breederveld

Can Vitamin C Prevent Complex Regional Pain Syndrome in Patients with Wrist Fractures?

A Randomized, Controlled, Multicenter Dose-Response Study

By P.E. Zollinger, MD, W.E. Tuinebreijer, MD, PhD, MSc, MA, R.S. Breederveld, MD, PhD, and R.W. Kreis, MD, PhD

<table>
<thead>
<tr>
<th>TABLE III Results of Logistic Regression Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
<tr>
<td>Cast-related complaints</td>
</tr>
<tr>
<td>Vitamin C overall</td>
</tr>
<tr>
<td>Vitamin C 200 mg</td>
</tr>
<tr>
<td>Vitamin C 500 mg</td>
</tr>
<tr>
<td>Vitamin C 1500 mg</td>
</tr>
</tbody>
</table>
"The Chicken - or - The Chicken Egg"
The mechanisms underlying CRPS are diverse.
Tawfik Laboratory

Rigorous science done by passionate people
# CRPS Diagnosis: Budapest Criteria

<table>
<thead>
<tr>
<th>Category</th>
<th>Symptoms (3 or more)</th>
<th>Signs (2 or more)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensory</td>
<td>Report hyperesthesia, Report alldynia</td>
<td>Hyperalgesia to pinprick, Alldynia to light touch, temperature, deep pressure, or joint movement</td>
</tr>
<tr>
<td>Vasomotor</td>
<td>Report temperature asymmetry, Report skin color change, Report skin color asymmetry</td>
<td>Temperature asymmetry (&gt; 1 degree Celsius), Skin color changes, Skin color asymmetry</td>
</tr>
<tr>
<td>Sudomotor</td>
<td>Report edema, Report sweating changes, Report sweating asymmetry</td>
<td>Edema, Sweating changes, Sweating asymmetry</td>
</tr>
<tr>
<td>Motor</td>
<td>Report decreased ROM, Report weakness, tremor, dystonia, Report trophic changes</td>
<td>Finding reduced ROM, Finding weakness, tremor, or dystonia, Finding trophic changes in hair, nail, or skin</td>
</tr>
</tbody>
</table>
Diagnostic Approach to CRPS?

Suspect CRPS:
1) Symptoms develop in relation to a limb trauma (usually within ~ 4-6 weeks)
2) Symptoms cannot be explained by the trauma any more
3) Symptoms affect the distal extremity, go beyond the trauma territory and beyond nerve/nerve root innervation territories
4) Other diseases are vigorously excluded

Are the diagnostic criteria (adapted IASP Budapest criteria) for CRPS fulfilled?

Symptom categories:
1) Hyperalgesia, "hyperesthesia", allodynia
2) Asymmetry of skin temperature and skin color
3) Asymmetry of sweating, edema
4) Reduced ROM beyond trauma joint, dystonia, tremor, weakness, changes of hair and nail growth

Diagnosis CRPS can be made if all 3 points are fulfilled:
1) Continuing pain
2) Report of ≥ 1 symptom from 3 out of the 4 above symptom categories in history
3) Display of ≥ 1 symptom from 2 out of the 4 above symptom categories at time of investigation

Use additional diagnostic tools if clinical diagnosis is doubtful or testimony is expected
1) Longterm or repetitive skin temperature measurement: side to side difference >1-2°C
2) Three-phase bone scintigraphy (TPBS) using 99mTc-DPD: Ribbon-like tracer accumulation distant from trauma site
3) Side-by-side X-ray: Spotty decalcification

Diagnosis “CRPS”

Differentiation
CRPS I: Without verified nerve lesion
CRPS II: With verified nerve lesion

Possible differentiation
"Primary warm": Skin temperature increased at the beginning ("inflammation type")
"Primary cold": Skin temperature decreased at the beginning (possibly poorer prognosis)
How do we distinguish the cause of peripheral pain?
How can imaging help the Pain Physician?

Pain is subjective
Physical exam does not always make the diagnosis clear
There are many peripheral nerves
An image is worth a thousand words...
MR Neurography- An Approach to “See” Pain?
Does an interdisciplinary team change treatment?

Etiology of Pain

- Pain Physician
- Physical-Therapist Psychologist
- Peripheral Nerve Surgeon
- Radiologist
- Neurologist/PM&R
Interdisciplinary evaluation of peripheral pain

- Patients seen in Pain Clinic or Ortho/Plastics “hand” clinic with limb pain
- Referred for MR neurography to evaluate possible peripheral nerve involvement
- Discussed at biweekly interdisciplinary “Nerve Team” conference
- Further work-up or management plans suggested
### TABLE 1 | Demographics and patient characteristics.

<table>
<thead>
<tr>
<th>Category</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of participants</td>
<td>58</td>
</tr>
<tr>
<td>Male</td>
<td>17 (29%)</td>
</tr>
<tr>
<td>Female</td>
<td>41 (72%)</td>
</tr>
<tr>
<td>Age current (years)</td>
<td>51 ± 16</td>
</tr>
<tr>
<td>Age at symptom onset (years)</td>
<td>44 ± 16</td>
</tr>
<tr>
<td>Female</td>
<td>42 ± 16</td>
</tr>
<tr>
<td>Male</td>
<td>48 ± 16</td>
</tr>
<tr>
<td>Duration of symptoms (years)</td>
<td>9 ± 16</td>
</tr>
<tr>
<td>Race</td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>44 (76%)</td>
</tr>
<tr>
<td>Asian</td>
<td>3 (5%)</td>
</tr>
<tr>
<td>Black or African American</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>Native Hawaiian or Pacific Islander</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>American Indian or Alaska Native</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>Other</td>
<td>5 (9%)</td>
</tr>
<tr>
<td>Unknown</td>
<td>4 (7%)</td>
</tr>
</tbody>
</table>

*Numbers are reported as n (%) or average ± standard deviation.*

### Characteristics of presentation

**TABLE 2 | Presenting features and inciting event.**

<table>
<thead>
<tr>
<th>Limb affected</th>
<th>% patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Upper (unilateral)</td>
<td>13 (22%)</td>
</tr>
<tr>
<td>Lower (unilateral)</td>
<td>38 (66%)</td>
</tr>
<tr>
<td>Upper (bilateral)</td>
<td>2 (3%)</td>
</tr>
<tr>
<td>Lower (bilateral)</td>
<td>5 (9%)</td>
</tr>
</tbody>
</table>

**Initiating event***

<table>
<thead>
<tr>
<th>Event</th>
<th>% patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgery</td>
<td>25 (43%)</td>
</tr>
<tr>
<td>Trauma (no fracture or diagnosed injury)</td>
<td>13 (22%)</td>
</tr>
<tr>
<td>Fracture</td>
<td>7 (12%)</td>
</tr>
<tr>
<td>Sprain</td>
<td>3 (5%)</td>
</tr>
<tr>
<td>Other</td>
<td>5 (9%)</td>
</tr>
<tr>
<td>Unknown</td>
<td>14 (24%)</td>
</tr>
</tbody>
</table>

*Numbers are reported as n (%).

*Several patients listed both “fracture and surgery” or “trauma and surgery” as their inciting event and therefore totals do not add up to 100%.*
Diagnostics performed

<table>
<thead>
<tr>
<th>Diagnostic test</th>
<th>% patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>MR neurography</td>
<td>58 (100%)</td>
</tr>
<tr>
<td>Nerve block</td>
<td>47 (81%)</td>
</tr>
<tr>
<td>EDX</td>
<td>26 (45%)</td>
</tr>
<tr>
<td>Standard MRI</td>
<td>24 (41%)</td>
</tr>
<tr>
<td>PET/MR study</td>
<td>15 (26%)</td>
</tr>
<tr>
<td>NMR bone scan</td>
<td>1 (2%)</td>
</tr>
</tbody>
</table>

Numbers are reported as n (%).
Findings on MR neurography

**TABLE 4** | MR neurography findings in all patients and in the subset who underwent surgery as a treatment option.

<table>
<thead>
<tr>
<th>Radiologic findings*</th>
<th>% patients</th>
<th>% patients who underwent surgery as a treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Signal alteration</td>
<td>35 (60%)</td>
<td>12 (57%)</td>
</tr>
<tr>
<td>Caliber change</td>
<td>15 (26%)</td>
<td>8 (38%)</td>
</tr>
<tr>
<td>Impingement/focal deviation/fat obliteration</td>
<td>13 (22%)</td>
<td>3 (14%)</td>
</tr>
<tr>
<td>Mass or mass-like lesion</td>
<td>4 (7%)</td>
<td>3 (14%)</td>
</tr>
<tr>
<td>Trauma/disruption</td>
<td>1 (2%)</td>
<td>1 (5%)</td>
</tr>
<tr>
<td>None</td>
<td>17 (29%)</td>
<td>5 (24%)</td>
</tr>
<tr>
<td>&gt;1 finding</td>
<td>22 (38%)</td>
<td>8 (38%)</td>
</tr>
</tbody>
</table>

*Note that there were 58 patients total and 21 patients who underwent surgery, however, a portion of patients met criteria for more than one radiologic finding and therefore totals do not add up to 100%. Numbers are reported as n (%).
**Team management changes diagnosis**

**TABLE 9 |** Comparison between referral diagnosis and diagnosis after nerve team evaluation.

<table>
<thead>
<tr>
<th>Referral diagnosis</th>
<th>CRPS I</th>
<th>CRPS II</th>
<th>CRPS NOS</th>
<th>Neuropathy*</th>
<th>Joint dysfunction</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRPS I</td>
<td>3</td>
<td>6</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>10</td>
</tr>
<tr>
<td>CRPS II</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>CRPS NOS</td>
<td>2</td>
<td>4</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>6</td>
</tr>
<tr>
<td>Neuropathy*</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>9</td>
<td>0</td>
<td>10</td>
</tr>
<tr>
<td>Neuropathy NOS</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Limb pain</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>5</td>
<td>1</td>
<td>8</td>
</tr>
<tr>
<td>Joint pain</td>
<td>0</td>
<td>5</td>
<td>0</td>
<td>7</td>
<td>0</td>
<td>12</td>
</tr>
<tr>
<td>Pain NOS</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>5</td>
<td>2</td>
<td>8</td>
</tr>
<tr>
<td>Total</td>
<td>7</td>
<td>19</td>
<td>0</td>
<td>29</td>
<td>3</td>
<td>58</td>
</tr>
</tbody>
</table>

*Neuropathy of a specified peripheral nerve. NOS, not otherwise specified.*

Values in bold and highlighted represent the diagnoses that did not change after interdisciplinary nerve team evaluation.
# Treatments provided

### TABLE 10 | Treatment and management.

<table>
<thead>
<tr>
<th>Intervention</th>
<th>% patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medication changes</td>
<td>55 (95%)</td>
</tr>
<tr>
<td>Physical/occupational therapy</td>
<td>45 (78%)</td>
</tr>
<tr>
<td>Pain psychology</td>
<td>45 (78%)</td>
</tr>
<tr>
<td>Intravenous infusion (e.g., Ketamine)</td>
<td>23 (40%)</td>
</tr>
<tr>
<td>Surgery</td>
<td>21 (36%)</td>
</tr>
<tr>
<td>Pulsed Radiofrequency neuromodulation</td>
<td>7 (12%)</td>
</tr>
<tr>
<td>Botox injection</td>
<td>7 (12%)</td>
</tr>
<tr>
<td>Cryoablation</td>
<td>6 (10%)</td>
</tr>
<tr>
<td>Spinal cord stimulator</td>
<td>6 (10%)</td>
</tr>
<tr>
<td>Peripheral nerve stimulator</td>
<td>5 (9%)</td>
</tr>
</tbody>
</table>

*Numbers are reported as n (%)*. 

---
Of patients who underwent surgery:

- 83% had positive findings on MRN
- 44% had more than one category of radiologic abnormality on MRN
- 100% had improvement in pain after ultrasound-guided block prior to surgery
I have CRPS and I need to have surgery: What do I do?

- **Work with your Pain Management physician and anesthesiologist** to develop a plan for managing post-operative pain
  - Increase or re-start anti-neuropathic medications (gabapentin, nortriptyline) the week prior to surgery and continue for 3-6 months after
  - Stop LDN 3-5 days prior to surgery
  - Consider Regional Anesthesia (nerve block)
  - Consider intra-operative and/or post-operative ketamine (if available)

- Take Vitamin C 500 mg daily x 50 days

- Start PT/OT when clinically stable/able
Specific diagnosis = Specific treatment
Treatment for CRPS *must* be multidisciplinary

- Medications
- Physical therapy
- Hand therapy
- Education
- Pain Psychology
- Interventions as appropriate

Medication options for CRPS:
- Steroids (early)
- Bisphosphonates (early)
- Anti-neuropathics
- Ketamine
- Low-dose naltrexone
- Other...

***Please consult your physician***
Targeting cortical representation: Physical therapy

- Effectiveness of physiotherapy interventions for pain and disability associated with CRPS type I and II

- 18 randomized clinical trials (RCTs) included with a total of 739 participants

- Lack of high-quality evidence

- Most included trials were at “high” risk of bias (either blinding not done, patients not randomly assigned...)

Smart et al. Cochrane Database of Systematic Reviews. 2016.
Targeting cortical representation: Physical therapy II

- Graded Motor Imagery (GMI)
  - 2 weeks of limb laterality recognition + 2 weeks of imagined movements + 2 weeks of mirror box therapy
- Four trials compared GMI to control interventions
- Overall improvements in pain and function reported immediately after the intervention and at 12-week follow-up

Smart et al. Cochrane Database of Systematic Reviews. 2016.
Targeting peripheral inflammation: Steroids

- **Steroids** decrease post-traumatic inflammation

- Probably most useful in the early/acute phase
  - within 6-9 months of initial injury

- No optimal dose reported
  - Prednisolone 100 mg per day with a 25% reduction q 4 days (Birklein et al. Neurology 2015)

- My practice has been *prednisone* three week taper starting with 6 tabs daily (30 mg) and decreasing by 1 tab daily q3 days (6 tabs daily x 3 days, 5 tabs daily x 3 days, 4 tabs daily x 3 day etc...) until off. (Atalay et al. Pain Physician 2014)

***Please consult your physician***
Targeting peripheral inflammation: Bisphosphonates

- **Bisphosphonates** reduce bone turnover
  - Shown most effective in early/acute phase
  - Within 1 year of initial injury
  - Highest efficacy in those with documented osteopenia
  - Also likely decrease CRPS-associated inflammation

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Biphosphonates Mean</th>
<th>Biphosphonates SD</th>
<th>Biphosphonates Total</th>
<th>Placebo Mean</th>
<th>Placebo SD</th>
<th>Placebo Total</th>
<th>Mean Difference IV, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adami 1997 (1)</td>
<td>36</td>
<td>0</td>
<td>10</td>
<td>48</td>
<td>6</td>
<td>10</td>
<td>-12.00 [-18.70, -5.30]</td>
</tr>
<tr>
<td>Manicourt 2004 (2)</td>
<td>18.11</td>
<td>3.6</td>
<td>20</td>
<td>47.5</td>
<td>2.9</td>
<td>20</td>
<td>-29.39 [-31.42, -27.36]</td>
</tr>
<tr>
<td>Robinson 2004 (3)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>Nt estimable</td>
</tr>
<tr>
<td>Varenna 2000 (4)</td>
<td>22.3</td>
<td>20.2</td>
<td>15</td>
<td>53.4</td>
<td>31.4</td>
<td>17</td>
<td>-34.10 [-52.19, -16.01]</td>
</tr>
</tbody>
</table>

35-40 mg daily x 8 weeks

***Please consult your physician***

Targeting central neuroinflammation: Ketamine

• **Ketamine** likely acts to decrease central excitatory signal

• **Schwartzman 2009**
  • Ketamine 0.35 mg/kg/hr over 4 hours x 10 working days
  • Stanford “outpatient protocol”

• **Sigtermans 2009**
  • Ketamine 22.2 mg/hr (mean) continuously for 4.2 days
  • Stanford “inpatient protocol”

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Mean (SD)</th>
<th>Total</th>
<th>Mean (SD)</th>
<th>Total</th>
<th>Weight</th>
<th>Mean Difference IV, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schwartzman 2009</td>
<td>6.06 (2.7)</td>
<td>9</td>
<td>7.61 (1.897)</td>
<td>10</td>
<td>11.2%</td>
<td>-1.55 [-3.67, 0.57]</td>
</tr>
<tr>
<td>Sigtermans 2009</td>
<td>2.68 (0.51)</td>
<td>30</td>
<td>5.45 (0.48)</td>
<td>30</td>
<td>88.8%</td>
<td>-2.77 [-3.02, -2.52]</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>39</strong></td>
<td><strong>40</strong></td>
<td><strong>100.0%</strong></td>
<td><strong>-2.63 [-3.39, -1.88]</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Tau² = 0.15; Chi² = 1.25, df = 1 (P = 0.26); I² = 20%
Test for overall effect: Z = 6.83 (P < 0.00001)
Targeting central neuroinflammation: Ketamine II

- My own anecdotal impression of ketamine:
  - About 1/3 of patients have no improvement
  - About 1/3 of patients have improvement during infusion, dissipates within minutes-hours of turning off infusion
  - About 1/3 of patients have lasting improvement
  - Those who ultimately get the most significant improvement are the ones who get relief at lower doses (10-25 mg/hr)
Targeting central neuroinflammation: LDN

- **Low-dose naltrexone (LDN)** may act on the TLR4 receptor on microglia to decrease neuroinflammation

- Standard dose is 50 mg, used for opioid addiction and alcohol dependence

- “Low dose” is 4.5 mg, needs to be compounded because standard tablet is 50 mg

  ***Stanford dose is LDN 4.5 mg at night, 2 hours prior to bedtime***

- Occasional start lower (1 mg at night) or go higher (maximum 9 mg at night)

  ***Please consult your physician***
Targeting central neuroinflammation: LDN II

LDN may be more effective for fibromyalgia with a fatigue component

Targeting the sympathetic nervous system: Sympathetic blocks

- Overactivity of the SNS is thought to contribute to CRPS
- Possible mechanism is through decreasing local sensitivity to epinephrine
- Reviewed 12 studies (n = 461 total)
- Overall quality of the evidence was low to very low with most studies showing no effect at follow up of local anesthetic sympathetic blockade
- Anecdotally I have had some luck doing these in “series”
  - 3 blocks each 3 weeks apart

Targeting the sympathetic nervous system: Sympathetic blocks II

- Patients received (in random order) lumbar sympathetic block with bupivacaine only vs. bupivacaine + 75 U Botox

Carroll I, Clark JD, Mackey SM. Ann Neurol. 2009.
Targeting the dorsal root ganglia: Neuromodulation

- 152 patients with CRPS in the lower extremities
- Primary end point: composite of safety and efficacy at 3 months, and subjects were assessed through 12 months for long-term outcomes and adverse events.
- Dorsal root ganglion stimulation also demonstrated greater improvements in quality of life and psychological disposition.
- Largest prospective, randomized comparative effectiveness trial to date, the results show that DRG stimulation provided a higher rate of treatment success with less postural variation in paresthesia intensity compared to SCS

Targeting the dorsal root ganglia: Neuromodulation

# Ongoing DRG clinical trials

<table>
<thead>
<tr>
<th>#</th>
<th>Recruiting Status</th>
<th>Study Title</th>
<th>Primary Conditions</th>
<th>Study Design and Methods</th>
<th>Sponsor/Location</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Recruiting</td>
<td>Comparative Study in Patients With Refractory Chronic Lower Limb Neuropathic Pain and/or Back Neuropathic Pain</td>
<td>Pain, Neuropathic</td>
<td>• Pain, Neuropathic&lt;br&gt;• Other: Spinal Cord Stimulation, association of both (DUAL), Dorsal Root Ganglion stimulation</td>
<td>Pitié-Salpêtrière Hospital, Paris, France</td>
</tr>
<tr>
<td>2</td>
<td>Completed Has Results</td>
<td>A Study to Confirm the Safety of High Frequency DRG Stimulator in Patients With Chronic Lower Limb Pain</td>
<td>Failed Back Surgery Syndrome, Complex Regional Pain Syndrome (CRPS)</td>
<td>• Failed Back Surgery Syndrome&lt;br&gt;• Complex Regional Pain Syndrome (CRPS)&lt;br&gt;• Device: G10 Medical MN 1000 External Stimulator</td>
<td>China Medical University Hospital, Taichung, Taiwan</td>
</tr>
</tbody>
</table>

- CRPS
- Discogenic Low Back Pain
- Failed Back Surgery Syndrome
- Neuropathic pain
- Peripheral Neuropathy
- Radiculopathy
Targeting autoimmunity: HCQ?

- There are likely autoimmune mechanisms underlying CRPS
  - Auto-antibodies to β2-AR and M2 muscarinic receptors found in CRPS patients
  - IgG from patients with CRPS can “transfer” symptoms to mice

- Some clinical data supports the use of steroids, IVIG (high dose), thalidomide and other immune modulators

- Hydroxychloroquine (HCQ) is an antimalarial and immunosuppressive used in the treatment of RA and SLE

***Please consult your physician***
Patients treated off-label with HCQ for refractory CRPS

Table 1
Clinical characteristics of patients prescribed HCQ for refractory CRPS.

<table>
<thead>
<tr>
<th>Patient number</th>
<th>Current age</th>
<th>Gender</th>
<th>Age at symptom onset (y)</th>
<th>Symptom duration (y)</th>
<th>CRPS type</th>
<th>HCQ duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>21</td>
<td>F</td>
<td>14</td>
<td>7</td>
<td>2</td>
<td>1 mo</td>
</tr>
<tr>
<td>2</td>
<td>40</td>
<td>F</td>
<td>35</td>
<td>4</td>
<td>1</td>
<td>7 mo</td>
</tr>
<tr>
<td>3</td>
<td>42</td>
<td>F</td>
<td>39</td>
<td>2</td>
<td>1</td>
<td>8 mo</td>
</tr>
<tr>
<td>4</td>
<td>62</td>
<td>F</td>
<td>55</td>
<td>6</td>
<td>2</td>
<td>9 mo</td>
</tr>
<tr>
<td>5</td>
<td>47</td>
<td>F</td>
<td>21</td>
<td>25</td>
<td>1</td>
<td>1.5 y</td>
</tr>
<tr>
<td>6</td>
<td>37</td>
<td>F</td>
<td>31</td>
<td>5</td>
<td>2</td>
<td>3 y</td>
</tr>
<tr>
<td>7</td>
<td>25</td>
<td>F</td>
<td>17</td>
<td>8</td>
<td>2</td>
<td>3 y</td>
</tr>
<tr>
<td>Avg (SD)</td>
<td>39 (13)</td>
<td>N/A</td>
<td>29 (14)</td>
<td>8 (8)</td>
<td>N/A</td>
<td>17 (14) mo</td>
</tr>
</tbody>
</table>

Avg, average; CRPS, complex regional pain syndrome; F, female; HCQ, hydroxychloroquine.

Haight E et al. Pain Reports, 2020
Summary

• CRPS most commonly occurs in the distal extremities after minor trauma or injury

• Looks like “usual healing” but inflammation and pain persist beyond expected timeframe

• Treatment must be multidisciplinary for best outcomes
The “Nerve Team”

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