CRPS-I: PREVENTION OF CHRONIC PAIN

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Complex Regional Pain Syndrome (CRPS)

1994 IASP Diagnostic Criteria:

1. A noxious event or cause of immobilization

2. Continuing or disproportionate pain, allodynia, or hyperalgesia

3. Edema, changes in skin blood flow, or abnormal sweating in the region of pain at some time in course

4. No other condition that could otherwise account for this degree of pain and dysfunction

CRPS-II refers to patients with known nerve injury (replaces causalgia)

CRPS-I refers to patients without known nerve injury (replaces reflex sympathetic dystrophy)

The phenotype is the same, the response to treatment is the same

Merskey H, Bogduk N eds. IASP Press, 1994
CRPS is a “pain plus” syndrome that affects the originally injured limb

Signs and symptoms worse distally

Microvascular dysregulation causes color and temperature asymmetry, edema

May have focal bone and joint changes

May have changes in muscle, skin, hair, nails
Some CRPS patients have movement disorders

Distal tonic dystonia is common

Also weakness, muscle atrophy, tremor, incoordination

Strong female predominance among CRPS/dystonia patients
CRPS epidemiology

- CRPS is a rare complication of trauma
- Rare in the elderly
- Strong female predominance (75-80%)
- Limb fractures a common cause
  30% of Colles wrist fractures or tibial fractures develop CRPS
- Evidence does not support consecutive phases (Veldman 1993)
- Children and teenagers almost always recover (Berde, Wilder)
- “Classical” cases are the most severe end of a spectrum. Mild cases are common in the community; and often resolve on their own (Sandroni 2003)
CRPS long viewed as a “Mystery Disease”

- Ill-defined constellation of symptoms
- Diverse causes - mostly traumatic
- No clear pathology or pathophysiology
  - Thought psychogenic by many, even today
- Symptom relief only treatment option, elusive
- No FDA-approved drugs for CRPS
- No pharmaceutical-sponsored or large trials
Mystery Disease

1. Identify cause of disease by studying patients
2. Create and validate animal models
3. Study pathogenesis in animal models

Pre-clinical trials
Candidate pathways for therapeutic intervention

Successful therapies?

Modified with permission from H. Zoghbi
Genetics: CRPS is a complex disorder

- HLA-DQ1 associated with CRPS-I (van de Beek, 2000)

- CRPS-I associated with Ehlers-Danlos, a collagen mutation that causes joint hyperflexibility (Stoler & Oaklander, 2006)

- EDS patients may have more trauma, more surgeries, nerves more vulnerable to stretch, penetration
Can GWAS provide target leads?

- CRPS is a complex disease (genes + environment)
- Strong environmental influence (injury) obscures genetic influence
- Clear genetic risk for post-traumatic neuralgia
  - Devor, Evidence for heritability of pain in patients with traumatic neuropathy PAIN, 2004
- Rare and usually transient phenotype – not enough patients
- Phenotyping difficult – no definition, no tests, no markers
New EMR epidemiology is more useful

• **Retrospective** EMR study of 600,000 Dutch patients found incidence 26.2 per 100,000 person/years (4x higher than Mayo study). Sex ratio of 3.4:1 and fracture as most common precipitant (44%)
  de Mos et al, PAIN 2007

• **Prospective** EMR study of comorbidities prior to CRPS onset linked CRPS with nerve injury, asthma, migraine, osteoporosis, NOT with somatization or psychiatric disease
  de Mos et al, PAIN 2008
CRPS-I likely a small-fiber predominant nerve injury

- Small-fiber polyneuropathies cause CRPS-like phenotype
- Same phenotype caused by nerve injuries in CRPS-II
- Neuro exam of CRPS-I patients usually reveals nerve injuries

Adult onset erythromelalgia: the small-fiber polyneuropathy phenotype that most resembles CRPS
Oaklander, Anesthesia & Analgesia, 2007

Novak, Autonomic impairment in painful neuropathy Neurology, 2001
Why might nerve injuries go unrecognized in CRPS-I?

• **CRPS patients not examined by nerve specialists**

• **Injuries to small-fibers difficult to diagnose**
  Do not cause weakness, muscle atrophy, or reduced reflexes
  EMG/NCS do not detect small fiber function
  Function usually preserved after partial nerve injuries

• **Patients with other diseases are commingled**
  Inflammation/infection (e.g. cellulitis)
  Small-fiber polyneuropathies
  Peripheral arterial disease
  Deep vein thrombosis
  Plexopathy
Pathological study of CRPS-I tissues shows chronic subtle axonal degeneration, worse in small-fibers

van der Laan, et al.
Complex regional pain syndrome type I (RSD): pathology of skeletal muscle and peripheral nerve. *Neurology*, 1998

Albrecht, et al.
Pathologic alterations of cutaneous innervation and vasculature in affected limbs from patients with complex regional pain syndrome. *PAIN*, 2006

Oaklander, et al.
PGP9.5+ skin biopsies from 18 CRPS-I patients showed 29% fewer small-fiber nerve endings in painful CRPS-affected area.

A control group of 7 symptom-matched osteoarthritis subjects who also had severe leg pain, edema, and disuse had no IENF loss, suggesting specific association with CRPS.
• Study of skin from amputated limbs of 2 end-stage patients

• Sweat glands and blood vessels are denervated and hypertrophied in CRPS-I skin

• Similar to changes seen in diabetic small-fiber polyneuropathy

• Likely causes other CRPS symptoms

Albrecht et al, PAIN, 2006
Trauma seems to sometimes preferentially damage small nociceptive axons

- Lack of myelin and saltatory conduction increases axonal energy needs
- Thin axons have high surface to volume ratio; more axolemma, less axonal transport

Sciatic transection in adult rats causes death of 37% of DRG cells by 32 weeks. Loss is earlier in and more severe in small, dark cells with unmyelinated axons than in large, light cells with myelinated axons

Cutting or crushing rat sciatic nerve does not reduce myelinated sensory axons in dorsal roots ... Unmyelinated axons were reduced by 50%
  Coggeshall et al. *Neuroscience*, 1997
Chronic CRPS may have different mechanisms than early CRPS

- Neurogenic microvascular dysregulation can cause chronic distal limb (and nerve) ischemia
- Injury to primary afferents triggers secondary changes in post-synaptic targets and network, including cortical plasticity
- Tertiary patient changes – inactivity, deconditioning, disuse and neglect syndrome, depression, poverty
3 opportunities to prevent chronic CRPS

A. Preventing the original trauma
   Preventing added iatrogenic trauma
      Unnecessary surgeries (knee arthroscopy)
      Tight casts, IVs, needlesticks

C. Preventing trauma/nerve injury from triggering early CRPS

D. Secondary intervention with disease-modifying treatment to prevent early CRPS from lingering into chronic CRPS
A few small placebo-controlled trials for early CRPS suggest disease-modifying effect, steroid trials have the best results of any

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<tr>
<th>Treatment</th>
<th>Efficacy</th>
<th>Trial (methods score)</th>
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<tbody>
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<td>Oral corticosteroids</td>
<td>Yes</td>
<td>Christensen, 1982 (71), Braus et al., 1994 (51)</td>
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<td>Yes</td>
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<td>Calcitonin</td>
<td>Yes</td>
<td>Gobelet et al., 1992 (80)</td>
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<tr>
<td></td>
<td>No</td>
<td>Bickerstaff, 1991 (82)</td>
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</table>

Supportive, non-placebo controlled trials of bisphosphonates, free-radical scavengers (including vitamin C)

from: Kingery, A critical review of controlled clinical trials for peripheral neuropathic pain and complex regional pain syndromes. *Pain* 73, 1997
Small, placebo-controlled trials of interventional treatments mostly negative, mean duration 3.5 weeks

<table>
<thead>
<tr>
<th>Drug</th>
<th>Route</th>
<th>Trial</th>
<th>(methods score)</th>
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<td>Yes</td>
<td>Glynn et al., 1981 (54)</td>
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<td>No</td>
<td>Rocco et al., 1989 (68),</td>
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<td>No</td>
<td>Blanchard et al., 1990 (71),</td>
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<td>Jadad et al., 1995 (68),</td>
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<td>No</td>
<td>Ramamurthy et al., 1995 (83)</td>
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<td>Droperidol</td>
<td>Intravenous regional block</td>
<td>No</td>
<td>Kettler, Abram, 1988 (44)</td>
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<td>Atropine</td>
<td>Intravenous regional block</td>
<td>No</td>
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<td>Bretylium</td>
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<td>Yes</td>
<td>Hord et al., 1992 (57)</td>
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<td>Ketanserin</td>
<td>Intravenous regional block</td>
<td>Yes</td>
<td>Hanna and Peat, 1989 (48)</td>
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<td></td>
<td>Intravenous</td>
<td>No</td>
<td>Bounnameaux et al., 1984 (45)</td>
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<td>Clonidine</td>
<td>Epidural</td>
<td>Yes</td>
<td>Rauck et al., 1993 (59)</td>
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<td>Phentolamine</td>
<td>Intravenous</td>
<td>Yes</td>
<td>Raja et al., 1991 (41)</td>
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<td></td>
<td></td>
<td>No</td>
<td>Verdugo, Ochoa, 1994 (52)</td>
</tr>
</tbody>
</table>

from: Kingery, A critical review of controlled clinical trials for peripheral neuropathic pain and complex regional pain syndromes. *Pain* 73, 1997
When to consider disease-modifying treatments

1. Use immediately post-trauma after high-risk traumas (eg radial head fx)

2. Use immediately post-trauma to high-risk patients (need to define)

3. Use within first weeks after trauma to patients with early CRPS to reduce risk of prolonged CRPS

4. Use in patients with chronic CRPS to speed healing

They may not be drugs (rehabilitation, neural stimulators, mirror therapy, hyperbaric oxygenation)
1. identify cause of disease by studying patients
2. create and validate animal models
3. pathogenesis studies in animal models

Mystery Disease

successful therapies?

pre-clinical trials

candidate pathways for therapeutic intervention

Disease Biology

modified with permission from H. Zoghbi
3 animal models of CRPS-I based on different CRPS causes:

**Chronic post-ischemia pain (CPIP)**

*Coderre, Xanthos, Francis, Bennett, PAIN, 2004*

O-ring on hindlimb of anesthetized rat for 3 h causes severe distal ischemia. Pain behaviors last at least 4 weeks in 70% of CPIP rats.

**BUT** all axons below o-ring degenerate, does not model partial axonal losses of CRPS-I patients

**Kingery rat tibia-fracture model** *PAIN, 2008*

Tibia fracture and 4 weeks of casting causes hindpaw warmth, edema, allodynia, and regional osteopenia. It causes primary sensitization, up-regulates local NGF, neuropeptide, and cytokines, and spinal cord Fos.

**BUT** this lesion does not reduce hindpaw innervation, does not model partial axonal losses of CRPS-I patients
Needlestick DNI:

We injure one distal sciatic branch with a single needlestick

Pre-mortem: pain behaviors measured on plantar hindpaws

Post-mortem: tissues gathered for biological testing

Half of rats develop long-lasting CRPS-like phenotype, half recover quickly from surgery (normal phenotype)

Anesthesia & Analgesia, 2007
Severity of distal axonal loss after 18g needlestick closely models the 29% average epidermal axon losses of CRPS-I patients

Skin from ipsilesional hindpaw shows mean loss of PGP9.5+ axons:
0% after 30G-needlestick
15% after 22G-needlestick
26% after 18G-needlestick

Anesthesia & Analgesia, 2007
Risk of developing evoked pain after needlestick is independent of lesion size

One tibial-nerve needlestick can cause hindpaw mechanical allodynia (≥ 51% drop in vF threshold)

Allodynia develops intraterritorially, extraterritorially, contralesionally

Anesthesia & Analgesia, 2007
CONCLUSION: Development of CRPS-I may require several “hits”

Neurogenic edema and inflammation within injured nerves may help magnify DNI into CRPS
Consider pooling CRPS and PTN for clinical trials

- CRPS microvascular dysregulation fluctuates from day to day and hour to hour
- CRPS regresses through PTN during healing
- Patients with PTN and CRPS respond to the same treatments
  - Rehab, medications and augmentative neurostimulation
- Consider classifying CRPS a “pain-plus” syndrome where patients may need treatment for neuralgia + other problems
Autoimmunity – A new player in CRPS?

• CRPS rare in elderly (c/w natural history of resolution) 
  elderly have reduced inflammatory response

• 75-80% female sex ratio
  women more prone to autoimmunity

• Comorbidity with asthma

• Limited evidence of autoantibodies against PNS in CRPS patients

• Corticosteroids effective in aborting chronic CRPS, what about NSAIDS?
Consider removing blockers of normal healing

• Children under age 5 do not develop neuropathic pain after nerve injuries ADD CITATION; older kids and teens develop acute but not chronic CRPS
• We evaluate non-recovering CRPS patients to find out why
  FOCAL INHIBITORS
  nerve ischemia from microvascular dysregulation
  ongoing nerve compression, traction, aberrant regeneration (neuroma)
  SYSTEMIC INHIBITORS
  of vascular perfusion (SMOKING, atherosclerosis) Tesfaye NEJM 2005
  of axonal regeneration (DM, thyroid, vit deficiency or excess, hep C)

• We encourage use and rehabilitation
  To help reverse cortical plasticity
  To lessen secondary sources of pain; deconditioning, obesity, depression
  To improve perfusion of damaged tissues and nerve
CRPS (and PTN) are monophasic insults that usually resolve on their own, like shingles. Why? Strong evolutionary pressures against pain persistence after injury.

- A 33-year old subject with CRPS for almost 5 months had severe pain and IENF loss (3% of control).
- She requested re-biopsy 9 months later for symptom resolution; this showed recovery of IENF to 95% of control, raising the question of whether recovery from CRPS is associated with successful axonal regeneration.

Whitley RJ, J Infectious Diseases, 1998
Best CRPS research subjects: Needlestick

Stereotyped location - medial or lateral cutaneous nerve of forearm
Stereotyped wound - needle diameter
Stereotyped effect - only axotomy
Samples entire population
Samples mostly healthy people without pre-procedure pain
Definite time of onset
Normal phenotype is no pain; abnormal phenotype easy to define
Highly organized collaborative group already established (Red Cross)
Patients seeking treatment, available for treatment trials
Subjects have already donated DNA!
Models many iatrogenic and military injuries
Rodent model already established


Drawbacks of needlestick nerve-injury model

A rare lesion; in 1/6300 blood donations (patients who filed reports)
Most injuries mild, may not meet full CRPS criteria
Rapid recovery for most

Politically difficult; Red Cross adverse to publicizing complications


Summary of new CRPS science

• CRPS has gone from “mystery pain” to predominantly neuropathic pain

• Evidence of distal nerve injury (DNI) in CRPS-I patients merges the subtypes

• These DNI disproportionately affect small-fibers

• Severity of nerve injury may not be major risk factor for CRPS development; likelihood of developing neurogenic inflammation may be more important