The Science and Mystery of CRPS

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CRPS Initiating Event
- Fracture, surgery, etc.
- Tissue damage
- Nerve injury (?)

Normal Healing

Acute “Warm CRPS”
- Duration < 1 year
- CRPS vs. Delayed Healing

Resolution

≈75% of patients within one year

Chronic CRPS
- Duration ≥ 1 year
- Transition to “Cold CRPS” (common)

Resolution in 30%
Stable in 54%
Deterioration in 16%

3-8% of patients

92-97% of patients

≈25% of acute CRPS patients

Adapted from: Bruehl (2015)
Is There a “Test for CRPS”?

• **2018 review paper:**
  – *No* definitive CRPS test
  – Multiple potentially useful biomarkers

• **2019 Valencia Meeting** – Possible biomarkers:
  – Degradation of Bradykinin (inflammatory mediator)
  – Osteoprotegerin (bone turnover marker)
  – IgG and IgM (immune marker)
  – microRNAs (miR-223, miR-338, and miR-548d)
  – *NOT* cytokines, bone scan, sensory testing, etc.
Who is At Risk for CRPS?

• “High CRPS risk” profile:
  – High acute pain intensity following injury
    • Support from multiple prospective studies
  – Female (3-4 times more common)
  – Middle-aged (≈50-70 years old)
  – Fracture (>40% of cases)
Who is At Risk for CRPS?

• Psychological factors are not a consistent predictor
  – CRPS is not a “psychogenic” condition
  – Theoretical model for psych-CRPS links

• Multiple studies show emotional distress has a stronger impact on CRPS pain than in other chronic pain conditions
  – Reflects physiology
  – Does NOT indicate pain is “all in your head”
CRPS Mechanisms Are Complex

**Big Question:**

*Cause CRPS vs. Associated with CRPS?*

Animal models can address causation (e.g., support for inflammatory factors)

*Bruehl, 2010; 2015*
QUESTION: Why is it so hard to make progress in treatment of CRPS?
Patient Meets Budapest Criteria...

- Peripheral Sensitization
- Central Sensitization
- Autonomic Dysfunction
- Altered Body Representation in the Brain
- Genetic Risk Factors
- Nerve Injury
- Inflammatory and Immune Changes

PATIENT 1
Patient Meets Budapest Criteria...
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- Peripheral Sensitization
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PATIENT 4
Inflammatory and Immune Mechanisms
Inflammation and CRPS

• Proinflammatory Cytokines and Neuropeptides
  – TNF-alpha, IL-1 beta, IL-2, IL-6
  – Substance P, calcitonin gene related peptide (CGRP), and bradykinin
  – Elevated in local blister fluid, circulating plasma, and cerebrospinal fluid in CRPS
  – Elevated in early CRPS, diminishes over first year

• Oxidative Stress (also can ➔ inflammation)?
  – Animal model of CRPS-I (IR model)
Immune System and CRPS

• Inflammation and immune system linked
• Autoimmune role suggested in CRPS
  • Anti-neuronal antibodies significantly elevated in 30 -40% of CRPS patients
  • Autoantibodies sensitize pain receptors
• “Passive transfer model” and IgG
Immune System and CRPS

• Treatment Implications?
  – Plasma exchange?
  – IVIG?
  – Immune modulating drugs?

• Small studies show possible benefit

• Mycophenolate trial (Goebel et al., 2018)
  – Effective overall (with several dramatic responders)
  – BUT - 45% stopped taking drug due to side effects
  – Larger trial and related trials planned
Genomics and CRPS
Genomics of CRPS

• **Genetics** – Reflects the DNA we were born with and never changes.
  – Inherited variations in genes *may* increase CRPS risk

• Strongest support for genetic risk factors:
  – CRPS clusters within families
  – Genetic differences in the human leukocyte antigen (HLA) system (underlies the adaptive immune response)

van Rooijen et al., 2012; de Rooij et al., 2009; van de Beek et al., 2003; Vaneker et al., 2002
Genomics of CRPS

- **Gene Expression** – How genes are translated into forming the actual proteins in your body.
  - DNA ➔ RNA ➔ Proteins
  - If you have a DNA signature that increases or decreases CRPS risk, actual risk only changes if that gene is turned on or off.

*Jin et al., 2013; Tan et al., 2017*
Genomics of CRPS

• Best evidence:
• Small study showing different gene expression in 4 CRPS patients compared to 5 non-pain controls

• Two of the top hits:
  • HLA gene (immune-related)
  • MMP9 gene (collagen-related)

Jin et al., 2013; Tan et al., 2017
Genomics of CRPS

• **Epigenetics** – Factors that can alter gene expression

• **DNA Methylation** – Can occur through genetic factors or environmental exposure. Alters gene expression. *These changes can be inherited and can impact on health even though the inherited DNA profile is unchanged*
Genomics of CRPS

• Best evidence:
  • RSDSA-funded study of military traumatic limb injury patients (+amputation)
    – N = 9 with CRPS (Budapest criteria)
    – N = 38 with non-CRPS neuropathic pain
• 48 genetic locations between groups showed significant differences in methylation (p<.001) despite similar pain intensity
• Replication for 7 of these methylation sites

Bruehl et al., 2019
Genomics of CRPS

• Top 2 methylation sites were in the \textit{COL11A1} and \textit{HLA-DRB6} genes (both less methylation)
  – \textit{HLA-DRB6} - immune-related
    • Same gene showed associations with CRPS in the only gene expression study
  – \textit{COL11A1} - regulates collagen formation (e.g., skin)
    • The only gene expression study also showed collagen-related differences in CRPS

\textit{Bruehl et al., 2019}
Functional Enrichment Analysis

Immune-Related
Implications?

• **Speculation:**
  - HLA system involved in autoimmune diseases
  - Maybe differential DNA methylation influences risk for CRPS via HLA-mediated autoimmune mechanisms?

• Implications for treatment mechanisms
CRPS Stages and Subtypes
Are There Progressive Stages of CRPS?

• Early CRPS expert proposed 3 sequential stages with different symptom patterns that all CRPS patients move through

• Cluster Analysis (Pattern Recognition) Study:
  – NO sequential stages, but ID’d 3 CRPS subtypes:
    • Limited + mostly neuropathic pain/sensory symptoms
    • Limited + mostly vasomotor symptoms (skin color/temp)
    • Classic severe CRPS/RSD with a variety of symptoms

• Similar results in a large Dutch study

Bruehl et al., 2002; de Mos et al., 2009
CRPS Subtypes: Warm vs. Cold CRPS

• Budapest discussions
  – Warm vs. Cold CRPS Subtypes? “Unproven”
• Large clinical study of 152 acute and chronic CRPS patients followed over 3 months
• Cluster analysis (pattern recognition):
  – Warm CRPS = warm/red skin, sweaty, swelling
  – Cold CRPS = cool/blue skin, less swelling

Bruehl et al., 2016
CRPS Subtypes: Warm vs. Cold CRPS

Warm = Acute
Cold = Chronic

Bruehl et al., 2016
CRPS Subtypes: Warm vs. Cold CRPS

Transition from warm to cold CRPS over time?
Treatment Implications
Drug Development Status

• Good News:
  – Orphan Condition status with FDA (and EMA)
  – Encourages drug development

• Bad News:
  – Multiple recent failed trials (1 still ongoing?)
  – Bisphosphonates, immune modulator

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School of Medicine
CRPS Complexity: TX Implications

• Problems:
  – Trials enroll “all CRPS patients”
  – Multiple CRPS mechanisms, and may differ between patients and over time
  – May be CRPS subtypes that respond and others that don’t (efficacy obscured by inclusion criteria?)
    • Recent trial results support this
  – Barrier to more CRPS trials = $$$$
Responses to Questions

For comprehensive CRPS overview, see: Bruehl S. Complex regional pain syndrome. *British Medical Journal*. 2015; 351: h2730. [available free online]
Question

Problem with the Budapest (IASP) Criteria – Sometimes I meet criteria and sometimes I don’t. Aren’t these criteria most appropriate only for an initial diagnosis [before treatment improves symptoms]?

• Valencia meeting in September 2019
• New diagnostic category for ICD 11?:
  – “CRPS with Remission of Some Features”
Question

Physicians question spreading – any evidence?

• Yes - it occurs, but unclear how often
• Little available research (biased?)
• Definition issue:
  – Real spread (Budapest criteria) vs. secondary myofascial pain vs. widespread pain (CS?)
• Some bilateral mechanism changes are noted even before spreading of symptoms
Question

• Patterns of spread (descending frequency):
  • Mirror-image spread (e.g., left to right)
  • Upper to lower limb (and vice versa)
  • Diagonal spread
  • All 4 limbs

• Occurs on average 19 mo. after initial onset
• 37-91% of spreading cases occur after second injury
Question

Is CRPS in children different than CRPS in adults? Physicians seem to treat childhood CRPS as more of a psychological condition.
Question

Any evidence that CRPS and Fibromyalgia are related?

• “Central Sensitization Syndromes”
  – Fibromyalgia
  – IBS
  – Migraine
  – Bladder pain
  – Others
Question

CRPS and Gastrointestinal Symptoms – “It has been suggested that CRPS is ‘doing something’ to my vagus nerve which controls the digestive system. Is this possible?”

• Heart rate variability studies:
  – Low vagal tone in CRPS (and most pain conditions)
  – Low vagal tone linked to digestive disorders
  – Address via abdominal breathing practice:
    • Breath in to count of 4, breath out to count of 6
Question

If CRPS occurs in the context of a nerve injury, and the nerve eventually regenerates, would CRPS be expected to improve?

• Specific nerve symptoms would resolve (numbness, tingling)
• Complex CRPS mechanisms, nerve injury only a small part (initial trigger?)
Is CRPS associated with sleep problems? Are there any ongoing studies?

• Our study in chronic back pain patients:
Question

What should a newly diagnosed CRPS patient know about treatments?

• Caveat….

• Nothing proven highly effective for CRPS patients across the board (no cure)
  – Not many good studies to show what works

• CRPS is complex ➔ multidisciplinary treatment

• SNS blocks used but no prolonged benefits
Question

• **Best evidence for:**
  – Antidepressant + Antiseizure medications
    • Low risk, moderately effective pain control options
    • Antidepressants improve sleep (= improved pain?)
  – Physical/Occupational Therapy and avoid disuse of affected limb in daily life
  – Corticosteroids *(early CRPS only)*
  – Stimulators: SCS and DRG *(NOT first line TX)*
  – Bisphosphonates?? *(maybe early CRPS only)*
Question

• Ketamine infusion may be effective

• May help even in chronic CRPS due to its mechanism of action (central sensitization)

• Any form of ketamine (e.g., even sublingual) might work if adequate blood levels can be achieved

• More intensive protocols (repetition) better?
  – Benefits for 12 weeks?

• Need to balance benefits with risks (cognitive, liver)
Any information on low dose naltrexone?

• No real clinical trials (one stuck in process)
• Small case report suggests may be effective
• Mechanism make sense
  – TLR4 receptor → microglial inflammation
• Reflects problem in CRPS literature: Many experimental therapies with little evidence
  – Potentially waste money on ineffective treatments
Question

Are opioid analgesics useful for CRPS?
• One study in CRPS patients (negative results)
• Carefully weigh benefits vs. costs/risks
• Problem with “opioid-induced hyperalgesia”
  – Snake chasing tale (vicious cycle)…..
• Daily diary study: opioids used for mood control as well as pain control
  – Better options for mood control?
Question

Could CRPS increase the risk of a “cytokine storm” if I am infected with COVID-19?

• Possible, but hard to say for sure....