DEBUNKING THE “SCIENCE” OF COMPLEX REGIONAL PAIN SYNDROME

......AND A FEW WORDS ABOUT CAUSATION ANALYSIS

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TAKE HOME POINTS

1. The CRPS CONSTRUCT is non-scientific and can not be proven.
2. Science published regarding this condition is weak.
3. An extensive differential diagnosis for this condition exists reflecting common, well recognized and treatable pathologic entities.
4. The appearance of this condition should be a “RED FLAG” for any clinician to begin the process of determining the underlying source of complaints.

CRPS I & II

• What is it?
• How is it defined?
• How do we prove its’ presence?
• Treatments?
• What are the outcomes?
• What is the science?

CRPS: THE PARADIGM

• Chronic pain “syndrome”
• Associated with trauma.....maybe
• “spontaneous” appearance
• No diagnostic tests
• Outcomes poor
• Treatments directed to syndromic complaints not scientifically supported
• No identified pathophysiology
• Maybe the Paradigm needs to go away....

COMPLEX REGIONAL PAIN SYNDROME: THE PARADIGM

Brief background
Transition from RSD to CRPS I, Causalgia to CRPS II
Diagnostic criteria
Diagnostic process
Differential diagnosis
Holes and Pitfalls

JOHN MILTON

PARADIGM LOST
SCIENCE AND MEDICINE

- How do we as medically trained physicians approach ANY clinical issue?
- HISTORY
- PHYSICAL EXAM
- Diagnostics
- Assessment and treatment
- Reassess, re-evaluate, re-examine
- After a suitable time frame, with treatment failure, start all over.....
- THIS IS OUR ONLY JOB IN LIFE

A FEW TERMS:

- OBJECTIVE (“SIGN”)
- SUBJECTIVE (“SYMPTOM”)
- PAIN
- VALIDITY
- RELIABILITY
- “INTER-RATER” vs. “INTRA-RATER” RELIABILITY
- “COIN TOSS”
- “SPASMS”/TRIGGER POINTS, TENDERNES
- RADICULOPATHY
- “SYNDROME” (HUMPTY DUMPTY)
- CAUSATION ANALYSIS

CAUSATION ANALYSIS

- A science
- Used to establish cause of pathology/disease processes
- Utilizes history, exam findings, objective medical findings to systematically address clinical processes leading to a disease state
- “Hill’s Criteria” named for Sir Austin Bradford-Hill, British Epidemiologist (smoking and lung cancer)

HILL’S CRITERIA

1. Temporal Relationship
2. Strength of Association (OR or RR, p value: the more likely the observed association is the true effect)
3. Dose Response (increased exposure, increased severity of response. The fundamental relationship in toxicology)
4. Replication of Findings (repeat studies in other population yield similar results)
5. Biologic Plausibility
6. Consideration of Alternate Explanations (DIFFERENTIAL DIAGNOSIS)
7. Cessation of Exposure
8. Consistency
9. Specificity of relationship

HILL’S CRITERIA

- To establish causation:
  1. Temporal Relationship (cause precedes effect)
  2. Strength of Association
  3. Dose Response
  4. Replication of Findings
  5. Cessation of Exposure
THIS IS SCIENCE......We use this to treat people.
Unproven hypothesis is not science......

DO WE KNOW WHO THIS IS?
OF COURSE....IT’S SANTA

• I KNOW IT (OR HIM.....)
  WHEN I SEE IT........

I KNOW IT WHEN I SEE IT... REALLY??

• This is Santa Clause
• We know where he lives
• We know what kind of a car he drives
• We know what he does on December 24th
• We know he watches us all the time. He knows what we’ve been thinking. He knows if we have been bad or good........
• We have no clue how he does it

• This is NOT SCIENCE....IT IS MAGICAL THINKING

SANTA’S AUTOBIOGRAPHY

• It is in print
• Therefore, it must be true......
• We will discuss this more ......
• Printed publications are not necessarily truthful
• Other cultural examples abound.....
• Easter Bunny, Tooth Fairy, The Great Pumpkin.....

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SOOOO....WHAT IS THIS CRPS?

• SYNDROME
• Descriptors can be found dating back to 16th century
• A chronic pain syndrome....?
• Approximately 100 names and almost as many diagnostic criteria(BORCHERS 2014)
• No clear cause but can be associated with “inciting event”
• Or.....maybe not
• No gold standard to prove its’ existence (think, pneumonia, HIV or stroke)
• No laboratory studies for confirmation (not even Bone scan)
• Condition may be diagnosed based solely on subjective complaints

HOW DID WE GET HERE?

Prior condition “RSD” or “Reflex Sympathetic Dystrophy”
Term abandoned (1994) as it was not scientifically or medically supportable. Clinical presentation was too inconsistent
The presentation was not always reflexive, associated with Sympathetic Nervous System or accompanied by Dystrophy
IASP (1994) abandoned “RSD” in favor of non-pathologic, generalized “Complex Regional Pain Syndrome” (CRPS)
Subdivided this into CRPS I and CRPS II
Criteria changed in a private, by invitation only meeting in Budapest 2004
CRPS I & II

- CRPS I designed to address nonspecific regional complaints.
- CRPS II addressed complaints following a nerve distribution.
- CRPS II designed to be similar to “Causalgia”.
- Diagnostic criteria established with significant overlap between CRPS I and II.
- The very nature of the construct does not permit equating RSD to CRPS 1. Continued use of term “RSD” means no reading or understanding of published medical literature since 1994.

CRPS DIAGNOSTIC CRITERIA (BUDAPEST CRITERIA 2004)

IASP diagnostic criteria for complex regional pain syndrome (CRPS)

1. The presence of an initiating noxious event, or a cause of immobilization.
2. Continuing pain, allodynia, or hyperalgesia in which the pain is disproportionate to any known inciting event.
3. Evidence at some time of edema, changes in skin blood flow, or abnormal sudomotor activity in the region of pain.
   * If seen without “major nerve damage” diagnose CRPS I; if seen in the presence of “major nerve damage” diagnose CRPS II.
4. This diagnosis is excluded by the existence of other conditions that would otherwise account for the degree of pain and dysfunction.

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CRITERIA 2 AND 3: (“CAN BE SIGNS OR SYMPTOMS”)

This means the examiner does NOT have to see these
Heightened local pain/sensitivity (“Allodynia”/“Hyperpathia”)
Abnormal sweat patterns
Temperature changes
Change in nail/hair/skin growth/appearance
Skin mottling/redness
Edema

“IT MUST BE RSD!!”
There is no FACTUAL BASIS on which to consider CRPS I. It cannot be proven as present based on science.
The “Paradigm” is no longer present

DYSAUTONOMIA

Autonomic nervous system (sympathetic) “FIGHT OR FLIGHT” controls skin temperature, hair/nail/sweat, GI, GU, etc.

DYSAUTONOMIA means the sympathetic system is malfunctioning.

Symptoms include abnormalities in sweat patterns, temperature of skin/limbs, peripheral blood flow, hair/nail skin growth changes abdominal pain, nausea/vomiting/cramps, chest pain, irregular heart beat, dizziness.

SOUND FAMILIAR???

SOME COMMON CAUSES OF DYSAUTONOMIA

Diabetes,
Nutritional deficits (OBESITY, Gastric Bypass)
Lupus, autoimmune conditions
Infections (Lyme disease, HIV)
Chronic alcoholism, chemotherapeutic agents
Irritable bowel syndrome, FMS, chronic fatigue
Crohn’s disease, ulcerative colitis
Cancer and paraneoplastic syndromes

SOUND FAMILIAR?

RETHINKING THE DIAGNOSTIC CRITERIA....HOW CAN THIS MAKE ANY SENSE???

No “injury”.....“inciting event”
Hill’s Criteria of Causation (and recognized science) cannot be applied, as there is no dose response, temporal relationship or biologic plausibility
Allodynia is exaggerated painful response to non-painful stimulus
Hyperpathia is exaggerated painful response to painful stimulus

These are SUBJECTIVE....but see often the basis for a conclusion
Historic information is adequate to satisfy criteria 2 and 3 with edema, color/temperature abnormalities, etc

It is possible to mimic ALL FINDING WITH IMMOBILIZATION

Exclusionary Criteria #4 requires a Differential Dx

I have never seen one performed
CRPS I DIFFERENTIAL DIAGNOSIS (PAINFUL LIMB)

**Hereditary nerve disorders**
- Toxic: (alcohol, lead, insecticides, solvents)
- Chemotherapeutics: (cancer drugs, antibiotics, steroids)
- Trauma: (cellulitis, entrapment neuropathy)
- Systemic: (lupus, RA, peripheral vascular disease, renal/liver failure, cancer and paraneoplastic syndromes, sarcoidosis)
- Infectious: (Hepatitis B and C, HIV, leprosy, Lyme disease, herpes simplex/cytomegalovirus, syphilis)
- Endocrine: (Diabetes, hypothyroidism, impaired glucose tolerance)
- GI: (Crohn’s disease, ulcerative colitis, celiac disease)

**Differential Diagnosis** (Consider Alternate Explanation)

**Nutritional/Metabolic**
- Vitamin deficiency (Vitamins A, B1, B6, B12, D, E, K)
- Trace minerals (copper, zinc, selenium)
- Small fiber neuropathy (diabetes, trauma, impaired glucose tolerance, inflammatory neuropathy, hepatitis, lupus, metabolic syndrome, etc.)

**It must again be noted that criteria 4 is required to be satisfied prior to establishing CRPS as present.**

**Non-Physical Causes**

- Somatoform disorders
- Anxiety
- Depressive disorders
- Bipolar disorders
- Personality Disorders
- Malingering
- Factitious Disorder
- See BARTH RJ, AMA guides newsletter

**Aberrant Disuse**

- An underlying physical and/or non-physical issue results in a minor event re-interpreted as major
- The injured person complains bitterly of pain (NORMAL VITAL SIGNS) and refuses to use the injured body part
- Swelling, redness, altered temperature and skin turgor with positive bone scan and x-ray changes can occur simply due to disuse
- The injured body part turns into a life changing issue, despite the lack of medical explanation (“Medically Unexplained Symptoms”)?

**Population at Risk??**

- Obese, hypertensive with hyperlipidemia
- Those with gastric bypass/major abdominal surgery
- Severe mental health issues (anxiety/depressive/personality disorder)
- Alcohol/tobacco abusers (peripheral vascular/liver disease)
- Nutritional deficiency (anorexia, major weight loss, severe systemic diseases)
- Autoimmune diseases (Lupus, RA, Sarcoidosis)
- Diabetics
- HIV, Hepatitis B and C

**CRPS I Typical Course**

**Minor injury/fracture/event**

Usual care
- Cascade of symptoms treated with cascade of ineffective procedures (injections, narcotics, drugs, SCS, more injections, more narcotics)
- No improvement

**Worsening Symptoms, Spreading to Other Extremities: “The RSD is Spreading”**

More treatment
- No differential diagnosis. No explanations

**This is a paradigm which needs to be lost**
CRPS AS A “DEFAULT CONDITION” ONLY

• No identified pathology
• No ability to prove diagnosis
• No differential diagnostic process
• Poor outcomes
• CRPS should only be provided after an extensive work up to rule out other diagnoses.

CRPS WORKUP PAINFUL PERIPHERAL NEUROPATHY/DYSAUTONOMIA

• BASIC: HISTORY and PHYSICAL EXAM
• CBC
• Fasting comprehensive metabolic profile with GGT
• ESR
• EMG
• UDS
• Mental health evaluation
• ANY ABNORMALITY, ESPECIALLY ABN SERUM GLUCOSE NEEDS MORE WORKUP
• WHY????

CRPS AS THE “DIAGNOSIS DU JOUR”

There is a good reason few people recover from this condition
It does not matter how many antibiotics you provide to a heart attack victim, they will NEVER respond. Antibiotics are the wrong drug for the provided diagnosis.

TREATMENT AND THE SCIENCE BEHIND IT

• PT….can help
• Sympathetic Blocks (Cochrane reviews: Moderate science they are of no value in diagnosis or treatment)
• Narcotics: No science to support value of long term narcotics for chronic benign pain. Now 130 deaths/day in US from narcotics
• Polypharmacy: No benefit as treatments are provided for unknown pathology
• Muscle relaxers/Gabapentin: maybe if has underlying neurologic disorder

OHIO BWC CROSS SECTIONAL CRPS ANALYSIS

• 2000-2011 780,000 claims
• Total 926 diagnosed with “RSD/CRPS
• Selected from the time from DOI to allowance of CRPS, looking for evidence of a baseline differential diagnostic process
• CBC, CMP, GGT, EMG, UDS, ESR, Psych
• NONE had a basic differential diagnostic profile done
• 31 dead, 94 PTD, 350 still on TT
• POOR OUTCOMES DUE TO INCOMPLETE WORKUP and Failure to diagnose

Sensitivity (a.k.a. True positive rate)
The statistical measurement of the proportion of positives correctly identified in a binary classification test for a condition or disease. Moreover, sensitivity measures the probability of a true positive or true disease present.

Specificity (a.k.a. True negative rate)
The statistical measurement of the proportion of negatives correctly identified in a binary classification test for a condition or disease. Moreover, specificity measures the probability of a true negative or true disease-free.

Sample binary, 2x2 classification test:

<table>
<thead>
<tr>
<th></th>
<th>Disease Present</th>
<th>Disease Absent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test Positive</td>
<td>a (True Positive)</td>
<td>b (False Positive)</td>
</tr>
<tr>
<td>Test Negative</td>
<td>c (False Negative)</td>
<td>d (True Negative)</td>
</tr>
</tbody>
</table>
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**CASE FOR CONSIDERATION**

- 42 yo WM, Date of injury 2002, injured right ankle descending from a ladder. Off work since. Diagnosed with “RSD” or “CRPS I”. Developed DVT with PE, vague GI complaints, BS elevation 200, “adrenal insufficiency, sleep apnea, hypogonadism, decreased testosterone, HTN, symptoms “spread” to all 4 extremities. He has lost all his teeth. He uses a motorized WC and crutches.
- Treatment involved multiple injections including sympathetic blocks, facet blocks, ESI, RFA all without benefit despite multiple repeats. Attempts at SCS unsuccessful.
- Meds include over 700 MED with Exalgos, Actiq suckers (1600 mcg 6x/day), Clonidine, 3 different testosterone preparations, multiple anti depressants including atypical antipsychotics

**SENSITIVITY**

\[
\text{Sensitivity} = \frac{\sum \text{True Positives (a)}}{\sum \text{True Positives (a)} + \sum \text{False Negatives (c)}}
\]

\[
\frac{a}{a+c} = \text{Probability of a positive test, given the patient has the condition/disease}
\]

**SPECIFICITY**

\[
\text{Specificity} = \frac{\sum \text{True Negatives (d)}}{\sum \text{True Negatives (d)} + \sum \text{False Positive (b)}}
\]

\[
\frac{d}{d+b} = \text{Probability of a negative test, given the patient does not have the condition/disease}
\]

**CRPS I ????**

- Review of polypharmacy include 12 major (potentially lethal) DDIs
- Despite all interventions, he reports increasing symptoms
- During course of exam lasting over 2 hours, he used 2 Actiq suckers
- SSDI granted in 2003
- Extensive lab/procedural requests were discussed. He discussed these with his attorney and refused. He continues to see his POR, travelling 2 hours for office visits and refills monthly.
- Diagnostic possibilities include RA, Lupus, Buerger's disease, addiction, somatoform disorder, anxiety, depressive disorder

**SPRAINED ANKLE AND CRPS I ????**
CRPS I IS A “DEFAULT CONDITION” ONLY!!!

- No pathologic explanation
- No confirmatory lab studies
- No “true positives”
- No scientific explanation
- No attempt at a differential diagnosis
- Medicine by Hubris
- Safety/health risks due to failure to diagnose,
- Treatment clearly unsafe and ineffective.
- PARADIGM LOST!!

WHAT IS THE DIAGNOSIS/PROGNOSIS?

- NOT CRPS!!!...no evidence of a differential diagnosis anywhere.
- Painful extremities with evidence of vascular compromise and dysautonomia (Subject for another discussion)
- Autoimmune condition heads the list
- Evidence of addiction/substance use disorder
- Urgent need to detox and discontinue harmful drug combinations
- Early demise of patient is predictable. Rules of the system provide very few options, but enforced continuation of harmful medications and combinations is lunacy.
- INSANITY IS DEFINED AS REPEATING THE SAME ACTION AND EXPECTING A DIFFERENT RESULT.

TAKE HOME POINTS

1. The CRPS CONSTRUCT is non-scientific and can not be proven
2. Science published regarding this condition is weak
3. An extensive differential diagnosis for this condition exists reflecting common, well recognized and treatable pathologic entities
4. The appearance of this condition should be a “RED FLAG” for any clinician to begin the process of determining the underlying source of complaints.

QUESTIONS AND COMMENTS

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