Mirror, Mirror on the Wall:  
Graded Motor Imagery to Treat CRPS  

Michael Bottros, MD
Learning Objectives

- Describe the Budapest criteria for the diagnosis of CRPS.
- Review the treatment options available for CRPS.
- List the components of Graded Motor Imagery in proper order.
Disclosures

- None

Outline

- History
- Epidemiology
- Clinical Presentation
- Proposed Pathophysiology
- Diagnosis and Differential
- Treatment
Causalgia

Silas Weir Mitchell
1829 - 1914

Philadelphia,
Lippincott, 1864
Causalgia

The term causalgia was coined at that time after the Greek words *kausis*, meaning burning, and *algos*, meaning pain.

Causalgia - Weir Mitchell

“Long after the trace of the effects of a wound has gone . . . neuralgic symptoms are apt to linger, and too many carry with them throughout long years this final reminder of the battle-field.”
Nerve Injuries: Lesions of Sensation

- Case 24: H.W. 42, shot in left arm, injured ulnar nerve
  - “50 days later-- Pain below elbow down into the hand, burning and tingling. . . It is intense and increasing.
  - Entire hand sore to touch. . . but tact is unimpaired.
  - The hand is swollen. . . the palm is red.
  - The patient has kept the hand wet ever since he was hurt.”

- Hyperaesthetic conditions
- Anesthetic conditions
- Neuralgia - Burning

Sudeck

- In 1900, Sudeck noted muscle atrophy and demineralization of bone:
  - Described as, "patchy osteoporosis of the small bones of the hands or feet and the distal metaphysis of the forearm or tibial bones."
  - This gave rise to the term Sudeck’s dystrophy.

Paul Sudeck
1866-1945
Leriche

- A lady, aged 37, receive a gift of a hare. She cut it up, with a view to make a well-known marinade. . . she pricked her index finger with a spicule of bone.
- “By next day, all trace of injury had vanished and it was forgotten. The hare was eaten, but it had its revenge!”

Post-Traumatic Spreading Neuralgia

- At the end of the week the pricked finger became painful. It felt as if on fire, yet there was no sign of inflammation. . .
- The slightest touch gave a disagreeable sensation.
- 2 months - She was in continuous pain . . . had undergone a complete change in her general character. She slept badly and ate very little.
Post-Traumatic Spreading Neuralgia

- The hand was moist and somewhat cold.
- The pricked finger... was rather redder than that of the other hand, and somewhat atrophied.
- Radiographically, there was... decalcification of the first phalanx.
- On several occasions I have made use of infiltrations of the stellate ganglia...
Complex Regional Pain Syndrome

- Does not consistently show sympathetic involvement, reflex mechanism, or dystrophy.

- Special Consensus Group of the International Association for the Study of Pain (IASP) termed *complex regional pain syndrome* in 1994:
  - Allows for a more broad inclusion showing varying levels of the disease process.

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Epidemiology
CRPS - Inciting Event
Restrospective Review - UW Pain Center

Epidemiology

- CRPS can occur at any age,
  - Pediatric patients constituting < 10%

- Common in younger adults
  - Mean 41.8 years
  - Mean age at time of injury 37.7 years
Epidemiology

- The incidence of CRPS (CRPS 1 and 2) estimated to be 6.28/100,000
- 2.3 - 3 times more frequent in females than males
- Usually involves a single limb in the early stage
- Mean duration of symptoms before pain center evaluation = 30 months

Estimated CRPS Cases per Year after Orthopedic Surgery

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Number/yr</th>
<th>Rate</th>
<th>CRPS /yr</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arthroscopic Knee surgery</td>
<td>657,000</td>
<td>2.3-4%</td>
<td>15-26,000</td>
</tr>
<tr>
<td>Carpal Tunnel</td>
<td>366,000</td>
<td>2.1-5%</td>
<td>8-18,000</td>
</tr>
<tr>
<td>Ankle fracture</td>
<td>257,000</td>
<td>13.6%</td>
<td>35,000</td>
</tr>
<tr>
<td>Total knee replace.</td>
<td>247,000</td>
<td>0.8-13%</td>
<td>2-32,000</td>
</tr>
<tr>
<td>Wrist fractures</td>
<td>194,000</td>
<td>7-37%</td>
<td>14-72,000</td>
</tr>
<tr>
<td>Fasciectomy-Dupuytren’s contra.</td>
<td>20,000</td>
<td>4.5-40%</td>
<td>1-8,000</td>
</tr>
<tr>
<td>TOTAL</td>
<td>1,741,000</td>
<td>4.3-11%</td>
<td>74-191,000</td>
</tr>
</tbody>
</table>

Gottschalk A, Raja SN Anesthesiology 2004
Severity Correlation

- There is no distinct correlation between the severity of trauma and the degree of CRPS symptoms.


Clinical Presentation
Clinical Aspects of CRPS

Sensory Changes in CRPS

- Allodynia
- Hyperalgesia
Pain Sensitization

Sensory Changes in CRPS
- Allodynia
- Hyperalgesia
- Hyperesthesia
  - Increased sensitivity to a sensory stimulation
- Hyperpathia
  - Abnormally exaggerated subjective response to painful stimuli
Autonomic Signs in CRPS

- Edema (80% of all cases)
- Color change
- Temperature (warmer or cooler – 80%)
- Sweating (↑ or ↓)

Motor Symptoms and Signs in CRPS

Tremor, Weakness, Contractures
Trophic Changes

- Altered nail growth
- Altered hair growth
- Skin changes

Signs & Symptoms in Early and Late CRPS

<table>
<thead>
<tr>
<th>Inflammatory S &amp;S</th>
<th>2-6 months</th>
<th>&gt;12 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain</td>
<td>88 %</td>
<td>97 %</td>
</tr>
<tr>
<td>Color difference</td>
<td>96 %</td>
<td>84 %</td>
</tr>
<tr>
<td>Edema</td>
<td>80 %</td>
<td>55 %</td>
</tr>
<tr>
<td>Temperature diff.</td>
<td>91 %</td>
<td>91 %</td>
</tr>
<tr>
<td>Limited movement</td>
<td>90 %</td>
<td>83 %</td>
</tr>
<tr>
<td>Pain with exercise</td>
<td>95 %</td>
<td>97 %</td>
</tr>
</tbody>
</table>

Total= 829 pts. Veldman et al. Lancet 1993;342:1012
Severe Complications of CRPS

Total of 74 patients

Psychological Changes

- Fear
- Anxiety
- Anger
- Suffering
- Depression
- Failure to Cope

Raja SN et al. Anesthesiology 2002
CRPS and the Psyche Facts and Fallacies

- CRPS is a psychiatric illness
- CRPS causes a psychiatric illness
- Psychiatric illness or personality disorder are predisposing factors for CRPS
- Psychological factors modify the course of CRPS
- Adjustment and function in CRPS are worsened by maladaptive behavior

Maleki J et al. 2000

CRPS Can Spread

- Contiguous Spread
  - Gradual, significant enlargement of the affected area
- Independent Spread
  - CRPS appears in a distant, non-contiguous area
- Mirror-Image Spread
  - Symptoms appear on the opposite side in an area that closely matches size and location of original side

Maleki J et al. 2000
Is CRPS a Systemic Disease?

A patient with both upper and lower extremity CRPS being affected at different times about two years apart.

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Pathophysiology
Pathophysiology

- Inflammation
- Autonomic Dysfunction
- Neuroplastic Changes in the CNS
- Ischemia/Reperfusion Injury

Pathophysiology

- Inflammation
  - Neurogenic
    - Substance P – plasma protein extravasation
    - CGRP – vasodilation
  - Inflammatory Cytokines (TNF-a, IL-2)
Pathophysiology

- Autonomic Dysfunction
  - Acute stage – sympathetic vasoconstrictor reflexes are inhibited
  - Chronic Stage – vasoconstriction and cold skin
  - Leads to impaired capillary nourishment

Pathophysiology

- Neuroplastic Changes
  - Ischemia/Reperfusion Injury

After 1 year of treatment

Central Nervous System Changes

- Chronic Pain is associated with generalized and regional reduction in gray matter
  - Not found in patients with acute pain

- Percent of atrophy is correlated with the duration of pain

Central Nervous System Changes

- Consistently altered in chronic pain: (Apkarian, 2004)
  - Cingulate cortex
    - Motivation & emotional response to pain
  - Insula
    - Estimation of the magnitude of pain
    - Awareness of body states
  - Dorsolateral prefrontal cortex
    - Integration of sensory input
    - Short-term working memory
Cortical thinning in CLBP compared to controls

Reversal of cortical thinning with treatment of pain

Reversal of cortical thinning with treatment of pain

Seminowicz, 2011
Diagnosis and Differential

Clinical Features of CRPS
IASP Diagnostic Criteria

- Presence of an initiating noxious event or reason for immobilization.
- Disproportional pain, allodynia, or hyperalgesia from a known inciting event.
- Signs or symptoms of any evidence showing edema, skin changes, blood flow, or abnormal sudomotor activity in the region of the pain.
- No other condition that would otherwise explain the degree of pain or dysfunction

IASP Diagnostic Criteria

- Developed in 1994
- Too vague
- How many symptoms?
- How many signs?
- Sensitivity for this diagnostic criteria was high: 0.98
- Unfortunately met with a low specificity: 0.36
- Lead to an over diagnosis of the pain syndrome
### Budapest Consensus Criteria 2007

**Must report** at least 1 symptom in 3 out of 4 categories

<table>
<thead>
<tr>
<th>Sensory</th>
<th>Vasomotor</th>
</tr>
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<tbody>
<tr>
<td>hyperesthesia and/or allodynia</td>
<td>Temperature asymmetry</td>
</tr>
<tr>
<td></td>
<td>Skin color changes</td>
</tr>
<tr>
<td></td>
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<table>
<thead>
<tr>
<th>Motor</th>
<th>Sudomotor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decreased ROM, tremor, weakness, dystonia, trophic changes (hair, nail, skin)</td>
<td>Edema</td>
</tr>
<tr>
<td></td>
<td>Sweating changes</td>
</tr>
<tr>
<td></td>
<td>Sweating asymmetry</td>
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**Must display** at least 1 sign in 2 or more categories

<table>
<thead>
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<tbody>
<tr>
<td>hyperalgesia and/or allodynia</td>
<td>Temperature asymmetry</td>
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<td>Skin color changes</td>
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<td>Decreased range of motion, weakness, tremor, dystonia, trophic changes (hair, nail, skin)</td>
<td>Edema</td>
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<tr>
<td></td>
<td>Sweating changes</td>
</tr>
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<td></td>
<td>Sweating asymmetry</td>
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Criteria Comparison

- IASP criteria showed high diagnostic sensitivity (0.98), but poor specificity (0.36).

- In comparison, the Budapest clinical criteria retained the exceptional sensitivity of the IASP criteria (0.99), but greatly improved upon the specificity (0.68).

Harden N et al. 2010
Treatment Options

- Anticonvulsants
- Antidepressants
- Alendronate
- Free Radical Scavengers
  - 50% dimethyl sulfoxide (DMSO) cream
  - Vitamin C
- Low Dose Naltrexone

Prevention of CRPS
Vitamin C (antioxidant) and Wrist Fractures

- 127 wrist fractures - 500 mg Vit C or placebo for 50 days
- 1 year followup - 4/54 (7%) in Vit C vs 14/65 (22%) in placebo developed CRPS

<table>
<thead>
<tr>
<th></th>
<th>Odds ratio</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fracture type</td>
<td>0.09</td>
<td>0.0037</td>
</tr>
<tr>
<td>Complaints in plaster cast</td>
<td>0.1</td>
<td>0.0002</td>
</tr>
<tr>
<td>Vit C therapy</td>
<td>4.22</td>
<td>0.04</td>
</tr>
</tbody>
</table>

Zollinger et al. Lancet 1999: 354; 2025
The typical dosage of LDN in published research is 4.5 mg.

Hypothesis: naltrexone operates via glial cells to exert beneficial actions. Dextro-naltrexone is a stereoisomer of naltrexone which is active at microglia receptors but has no activity on opioid receptors.
Treatment Options

- Baclofen
- Calcitonin – conflicting data
- Vasodilatory drugs – No evidence
  - Ex. Verapamil, ketanserin

Do Nerve Blocks Help in the Diagnosis of CRPS?

- Sympathetic nerve blocks help identify the subset of patients with sympathetically mediated pain.
Stellate Ganglion Block

- Esophagus lateral to airway in 50% and 74% of the subjects at C6 and C7.
- Esophagus covered more than half of the distance between the airway and the carotid artery in 14% and 44% of the subjects at the C6 and C7 levels.
- Via anterior approach, a major vessel was observed in up to 29% and 43% of patients at the C6 and C7 levels.

References:
- Pain Practice 2008, 8(4): 226-240
If I have CRPS, can I undergo surgery without the recurrence of disease?

Retrospective Analysis
4-16 months after CRPS
2 separate surgeons
SGB post-surgery
One year follow-up

Treatment Options

- Sympathectomy
  - Concerns for post-sympathectomy pain syndrome
- Spinal Cord Stimulation
  - Significant reduction in pain at 6, 12, and 24 months after implantation
Physical Therapy

Graded Motor Imagery

[Diagram showing processes and steps of motor imagery]
Limb Laterality

Right or Left?

[Images of hands and foot]
Right or Left?

Explicit Motor Imagery
Mirror Therapy

Graded Motor Imagery

- Sequential activation of cortical pre-motor and motor networks
- Laterality and Imagery = pre motor
- Mirror Therapy = Primary Motor Cortex and S1 cortices
- Reversal of cortical reorganization
Results

- Opioid use: following the treatment process, overall there is a significant reduction in opioid use, p<0.001.
  - Pre GMI: 48 of 92
  - Post GMI 19 of 92
- Functional improvement: following GMI, there is a significant improvement in functionality
  - Median improvement of 32% on quick DASH, p<0.001
  - Median improvement of 22.5% on LEFS, p<0.001
- NRS Scores: Median scores showed significant improvement, p<0.001
  - Pre GMI: 6/10
  - Post GMI: 3.2/10

Conclusions

- CRPS remains an enigmatic condition.
- Not all patients have the same set of symptoms.
- As it persists, the focus moves toward rehabilitation.
- Treatment with GMI significantly impacts degree of functional recovery and pain improvement in CRPS.