Disclosures

- Nothing to disclose
Learning Objectives

- Identify pain patients who have central pain
- Identify the presence of complications
- Formulate a comprehensive treatment plan
Central Pain Definition

- “Constant pain that is driven by a focus inside the brain and characterized by stimulation of the sympathetic nervous and endocrine systems”
Common Central Pain Conditions

- Centralized from a peripheral nerve injury
- Direct brain injury
  - TBI
  - Post-stroke
  - Post-infections
  - Multiple sclerosis
- Originates inside brain from autoimmunity, genetics, or unknown
  - Fibromyalgia
  - Vulvodynia
  - Interstitial cystitis
Terminology

- **CLASSICAL CENTRAL**: Only referred to brain injury such as a stroke
- **NEUROPATHIC**: Pain persists after initiating injury is cured
- **CENTRALIZATION**: Process of glial cell activation, neuroinflammation, and imbedding of pain memory
- **SENSITIZATION**: Over-reaction by the brain to painful stimuli
- **NEUROPLASTICITY**: Reformation of rebuilding of nerve tissue
Central Pain May Be:

- Mild
- Moderate
- Severe
CHRONIC PAIN PATIENTS MAY SIMULTANEOUSLY HAVE CENTRAL AND PERIPHERAL COMPONENTS
Diagnosis of Centralized Pain

- Made by history and physical examination
- Laboratory tests are supportive – NOT confirmatory
Time for Centralization to Occur Post Injury

- Can be immediate with sudden injury
- Usual – about 6 to 8 weeks post-surgery
- Can be delayed after injury and suddenly occur
- Patient example: “It took me over”
How Central Pain Develops

INJURY TO PERIPHERAL OR CENTRAL NERVE TISSUE

CHEMICAL AND/OR ELECTRONIC SIGNALS ENTER CNS

MICROGLIAL CELL ACTIVATION

NEUROINFLAMMATION

RELEASE OF EXCESS GLUTAMATE/NEUROTOXINS

CELL DEATH, APOPTOSIS, REFORMATION

METABOLIC DISTURBANCES

PAIN, DEPRESSION, MENTAL DYSFUNCTION
Glial Activation

NORMAL

ACTIVATION

A

B

Courtesy of Practical Pain Management
Pathologic Results Of Over-activated Glial Cells

- Insomnia
- Central Pain
- Hormone Over-stimulation
- Over-activated Glial Cells
- Neuroinflammation
- Over-stimulation of the sympathetic nervous system
- Intellectual Decline
- Chronic Fatigue
- Depression
Variations in Glial Cell Inflammatory Sites

- Size
- Neuroanatomical location
- Metabolic disturbances
- Clinical manifestations
- Cellular destruction

*The site may progressively enlarge and produce cellular dysfunction and/or destruction.
CNS Cellular Characteristics

- Progressive
- Inflammatory
- Tissue destructive
- Must be considered a severe chronic disease
  with a tragic outcome

How Pain Stimulates Hormones
Uncontrolled pain can deplete pituitary, adrenal, and gonadal hormones.
Common Clinical Characteristics of Central Pain
Major Symptoms

- Constant pain
- Insomnia
- Depression
- Fatigue
Sympathetic Nervous System Stimulation

- Hypertension
- Tachycardia
- Hyperthermia
- Hyperhidrosis
- Mydriasis
- Hyperreflexia
- VASOCONSTRICTION (Cold Hands/Feet)
Secondary Symptoms

- Anxiety
- Anorexia
- Hopelessness
- Allodynia
Behavior

- Reclusivity
- Immobility
- Becoming house bound
## Centralized Pain Screening N=57

<table>
<thead>
<tr>
<th></th>
<th>Question</th>
<th>Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Is your pain constant (&quot;never leaves&quot;)?</td>
<td>51 (89.5%)</td>
</tr>
<tr>
<td>2</td>
<td>Do you have insomnia?</td>
<td>48 (84.2%)</td>
</tr>
<tr>
<td>3</td>
<td>Do you have periods of great sweating?</td>
<td>43 (75.4%)</td>
</tr>
<tr>
<td>4</td>
<td>Do you have periods when your temperature goes up (feel hot)?</td>
<td>44 (77.2%)</td>
</tr>
<tr>
<td>5</td>
<td>Are your hands and/or feet usually cold?</td>
<td>44 (77.2%)</td>
</tr>
<tr>
<td>6</td>
<td>Do you have periods that you have difficulty reading, analyzing, or remembering?</td>
<td>37 (64.9%)</td>
</tr>
</tbody>
</table>
## Centralized Pain Screening N=57

<table>
<thead>
<tr>
<th></th>
<th>Question</th>
<th>Yes (N=57)</th>
</tr>
</thead>
<tbody>
<tr>
<td>7</td>
<td>Do you have periods when you can’t smell, taste, or hear?</td>
<td>17 (29.8%)</td>
</tr>
<tr>
<td>8</td>
<td>Do you sometimes have a lot of electricity? (Shocks others, burn out lights or watches)</td>
<td>29 (50.9%)</td>
</tr>
<tr>
<td>9</td>
<td>Are you always fatigued even if you get some sleep?</td>
<td>43 (75.4%)</td>
</tr>
<tr>
<td>10</td>
<td>Does some of your pain move from one location to another?</td>
<td>39 (68.4%)</td>
</tr>
<tr>
<td>11</td>
<td>Do you have jerking or tremors?</td>
<td>41 (71.9%)</td>
</tr>
<tr>
<td>12</td>
<td>Does the skin over your pain site really hurt if you touch or rub it?</td>
<td>39 (68.4%)</td>
</tr>
</tbody>
</table>
Search for Biomarkers of Central Pain
### Biomarker Search in 80 Centralized Pain Patients in On-going Medical Management

<table>
<thead>
<tr>
<th></th>
<th>Inflammatory Biomarkers</th>
<th>No. % with Elevations</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Alpha 1 antitrypsin</td>
<td>14 (17.5%)</td>
</tr>
<tr>
<td>2</td>
<td>Myeloperoxidase</td>
<td>24 (30.0%)</td>
</tr>
<tr>
<td>3</td>
<td>Soluble tumor necrosis factor alpha receptor II</td>
<td>20 (25.0%)</td>
</tr>
<tr>
<td>4</td>
<td>Erythrocyte sedimentation rate</td>
<td>22 (27.5%)</td>
</tr>
<tr>
<td>5</td>
<td>C-reactive protein</td>
<td>26 (32.5%)</td>
</tr>
</tbody>
</table>
Biomarker Search in 80 Centralized Pain Patients in On-going Medical Management (cont’d)

<table>
<thead>
<tr>
<th>METABOLIC BY-PRODUCTS</th>
<th>NO. % WITH ELEVATIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>Brain derived neurotrophic factor</td>
</tr>
<tr>
<td>7</td>
<td>Resistin</td>
</tr>
<tr>
<td>8</td>
<td>Apolipoprotein</td>
</tr>
</tbody>
</table>
### Biomarker Search in 80 Centralized Pain Patients in On-going Medical Management (cont’d)

<table>
<thead>
<tr>
<th></th>
<th>HORMONES FROM HPA AXIS</th>
<th>NO. % WITH ELEVATIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>9 Cortisol</td>
<td></td>
<td>2 (2.5%)</td>
</tr>
<tr>
<td>10 Prolactin</td>
<td></td>
<td>11 (13.8%)</td>
</tr>
<tr>
<td>11 Epidermal growth factor</td>
<td></td>
<td>5 (6.3%)</td>
</tr>
<tr>
<td>Patients with at least one elevated biomarker</td>
<td></td>
<td>53 (66.3%)</td>
</tr>
<tr>
<td>Patients with 2 or more elevated biomarkers</td>
<td></td>
<td>25 (31.3%)</td>
</tr>
</tbody>
</table>
## Search for Hormone Abnormalities in 61 Uncontrolled Central Pain Patients

<table>
<thead>
<tr>
<th>HORMONE</th>
<th>NO. TESTED</th>
<th>NO. ABNORMAL*</th>
<th>NO. HIGH</th>
<th>NO. LOW</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACTH</td>
<td>55</td>
<td>15 (27.3%)</td>
<td>5 (9.1%)</td>
<td>10 (16.4%)</td>
</tr>
<tr>
<td>PREGNENOLONE</td>
<td>50</td>
<td>11 (20.8%)</td>
<td>2 (1.9%)</td>
<td>14 (28.0%)</td>
</tr>
<tr>
<td>DHEA</td>
<td>43</td>
<td>16 (37.2%)</td>
<td>2 (1.9%)</td>
<td>14 (32.6%)</td>
</tr>
<tr>
<td>TESTOSTERONE</td>
<td>59</td>
<td>22 (37.2%)</td>
<td>3 (5.1%)</td>
<td>19 (32.2%)</td>
</tr>
<tr>
<td>CORTISOL</td>
<td>61</td>
<td>20 (32.8%)</td>
<td>10 (16.4%)</td>
<td>10 (16.4%)</td>
</tr>
<tr>
<td>PROGESTERONE</td>
<td>53</td>
<td>11 (20.8%)</td>
<td>2 (1.9%)</td>
<td>9 (17.0%)</td>
</tr>
</tbody>
</table>

No. with an abnormality was 49 (80.3%)
Aggressive Medical Treatment May Be Required

- Neuropathic agents
- Antidepressants
- Bedtime sedatives
- Anti-inflammatory agents
- Stimulants
- Anti-anxiety/benzodiazepines
- Opioids
- Neurohormones
Basic Treatment Support

- Vitamins B12, C, D
- Diet with adequate protein and anti-inflammatory foods
- Physical exercise to increase O2
- Mental/social activity
Basic Treatment Support (cont’d)

- Anti-inflammatory agents
  - Curcumin (diarylheptanoid)
  - Tumeric
  - Fish oil
  - White willow bark
  - Aspirin
Basic Treatment Support (cont’d)

- Electromagnetic therapies
  - Copper
  - Magnets
  - Micro electric current
  - Electromagnetic energy wave
Basic Treatment Support (cont’d)

- Hormone replacement
- Treat peripheral sites if still painful

• NOTE: The above measures are the presenter’s pain management regimen, and no claims of cure or effectiveness are made
Stimulants in Centralized Pain

- Usually needed in severe cases
- Seems counterintuitive since excess sympathetic-efferent discharge
- Administration usually stops sympathetic discharge, allodynia, and hyperalgesia
- Reason? Decreased dopamine and norepinephrine?
- Agents: Dextroamphetamine, methylphenidate, phentermine, modafanil
Neurohormones

- Pregnenolone
- Progesterone
- Human chorionic gonadotropin
- Oxytocin
Glial Cell Inhibitor

MINOCYCLINE

Good response in some patients
TREATMENT EFFECTIVENESS SHOULD BE OBJECTIVELY DETERMINED BY HORMONE AND INFLAMMATORY BIOMARKERS
References

- Coyle DE. Partial peripheral nerve injury leads to activation of astroglia and microglia which parallel the development of alldynic behavior. Glia. 1998;23:75-83.
References (cont’d)

References (cont’d)

References (cont’d)

- Tracey I, Bushnell CM. How neuroimaging studies have challenged us to rethink is chronic pain a disease? J Pain. 2009;10(11):1113-1120.