Introduction to Pain

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Clinical Cases

• 63 year old white female presents to the emergency room with an acute outbreak of shingles following a recent episode of flu. She reports some itching at the site of the rash (lower right side of her trunk) that has progressed into a burning/stabbing pain (7/10) over the past two days.

• A 23 year old African-American male presents to the ER claiming to be having an acute sickle cell crisis. He is visible agitated and reports that his pain is a 10/10 and wants an injection of 150 mg of Demerol (meperidine).

• A 38-year-old man (70 kg) suffered for 48 h from an acute pain in the lumbar region that was not improved with common drugs available at home (acetaminophen 1000 mg3/day). The pain was paroxystic with no analgesic position. The patient reported a previous history of renal acute pain. Clinical examination showed a maximal pain to pressure of the right lumbar region, a microscopic haematuria, no elevated temperature, and VAS or NS equal to 5 (0=no pain, 10=maximal pain). The X-ray of the abdomen showed a small opaque object in the projection of the fourth right lumbar vertebra. The ultrasonographic exam showed a moderate dilatation of the right urinary
Introduction to Pain

- Pain is defined by the International Association for the Study of Pain (IASP) as “an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage”

- Physiological pain serves an important protective and reparative function
Congenital insensitivity to pain with anhidrosis (CIPA): the spectrum of radiological findings


Congenital Insensitivity to Pain with Anhidrosis (CIPA) in Israeli-Bedouins: Genetic Heterogeneity, Novel Mutations in the TRKA/NGF Receptor Gene, Clinical Findings, and Results of Nerve Conduction Studies

Sharon Shatzky,¹ Shimon Moses,² Jacov Levy,³ Vered Pinski,³ Eli Hershkovitz,³ Laura Herzog,² Zamir Shorer,² Anthony Luder,⁴ and Ruti Parvari¹*
Peripheral Nerve Fibers

Aα

C

Ad
<table>
<thead>
<tr>
<th>Feature</th>
<th>Number affected</th>
<th>% Affected</th>
</tr>
</thead>
<tbody>
<tr>
<td>Loss of sensitivity to pain</td>
<td>28/28</td>
<td>100</td>
</tr>
<tr>
<td>Self mutilation</td>
<td>26/28</td>
<td>92</td>
</tr>
<tr>
<td>Poor wound healing</td>
<td>14/28</td>
<td>50</td>
</tr>
<tr>
<td>Osteomyelitis</td>
<td>11/28</td>
<td>39</td>
</tr>
<tr>
<td>Limb amputation</td>
<td>15/28</td>
<td>53</td>
</tr>
<tr>
<td>Recurrent infections</td>
<td>15/28</td>
<td>53</td>
</tr>
<tr>
<td>Unexplained fever</td>
<td>28/28</td>
<td>100</td>
</tr>
<tr>
<td>Lack of sweating</td>
<td>28/28</td>
<td>100</td>
</tr>
<tr>
<td>Corneal ulceration</td>
<td>12/28</td>
<td>43</td>
</tr>
<tr>
<td>Mental retardation</td>
<td>27/28</td>
<td>96</td>
</tr>
<tr>
<td>Charcot joints</td>
<td>2/28</td>
<td>7</td>
</tr>
<tr>
<td>Anemia</td>
<td>22/28</td>
<td>79</td>
</tr>
<tr>
<td>Deceased</td>
<td>5/28</td>
<td>17</td>
</tr>
<tr>
<td>Nerve conduction studies</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal motor velocity</td>
<td>13/13</td>
<td>100</td>
</tr>
<tr>
<td>Normal sensory velocity</td>
<td>13/13</td>
<td>100</td>
</tr>
<tr>
<td>Abnormal sympathetic skin response</td>
<td>13/13</td>
<td>100</td>
</tr>
<tr>
<td>Mutation studies</td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>TrkA: 1926-ins-T</em></td>
<td></td>
<td>16 families</td>
</tr>
<tr>
<td><em>TrkA: Pro-689-Leu</em></td>
<td></td>
<td>1 family</td>
</tr>
<tr>
<td>Different gene</td>
<td></td>
<td>1 family</td>
</tr>
</tbody>
</table>
QuickTime™ and a TIFF (Uncompressed) decompressor are needed to see this picture.
Normal

Protective

Acute → Prolonged

Reflexes

Inflammation and Repair

Abnormal

Non-protective

Chronic (Pain as Disease)

Healing of injured tissue can occur but pain continues

Therapeutic goal:
return sensitivity to normal thresholds without loss of protective function (anti hyperalgesia/anti-allodynia)
Impact of Chronic Pain

• In contrast to normal pain states, pathological chronic pain serves no apparent purpose.

• Furthermore it poses significant health and social problems in the United States and elsewhere:
  - quality of human life
  - economic costs
## Incidence and Cost of Various Neurological Disorders

<table>
<thead>
<tr>
<th>Disease</th>
<th>Cases</th>
<th>Cost</th>
<th>Cost/Case</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic Pain</td>
<td>90 million</td>
<td>$100 billion</td>
<td>$1,100</td>
</tr>
<tr>
<td>Addiction</td>
<td>30 million</td>
<td>$160 billion</td>
<td>$5,333</td>
</tr>
<tr>
<td>Alzheimer’s</td>
<td>4 million</td>
<td>$90 billion</td>
<td>$22,500</td>
</tr>
<tr>
<td>Stroke</td>
<td>3 million</td>
<td>$25 billion</td>
<td>$8,333</td>
</tr>
<tr>
<td>Schizophrenia</td>
<td>2 million</td>
<td>$32.5 billion</td>
<td>$16,250</td>
</tr>
<tr>
<td>Parkinson’s</td>
<td>0.5 million</td>
<td>$6 billion</td>
<td>$12,000</td>
</tr>
<tr>
<td>Spinal Injury</td>
<td>0.3 million</td>
<td>$10 billion</td>
<td>$33,000</td>
</tr>
</tbody>
</table>

*National Institutes of Health, 1998*
Processing of Pain Signals

- **Transduction** - Noxious stimuli are converted to electrical signals in sensory nerve endings

- **Transmission** - neural events which relay the information from the periphery to the cortex

- **Modulation** - the nervous system can selectively inhibit the transmission of pain signals

- **Perception** - subjective interpretation by the cortex of the noxious stimulus.

  - Sensory component
Relay and Descending Modulation

Cortex

Thalamus

Central Perception

Transmission

Signal Transduction

Brain Stem

Peripheral stimulus

Spinal Cord
Descending Modulation in Chronic Pain States

“Top-down” Modulation

Pain is a Sensory Experience
- Emotion
- Attention/Distraction
- Expectation
- Stress

Ascending Transmission
- Novel Therapies

Aδ or C

Nociceptive drive
The Variability of Pain

- **Pain Detection Threshold**
  - a property of the sensory system
  - highly reproducible in individuals

- **Pain Tolerance**
  - Highly variable among individuals
  - dependent on affective components
Neural Mechanisms of Pain Transduction and Transmission

Transduction: Pain stimulus is converted into a neural signal at the peripheral endings.

Conduction: Neural signal travels along the sensory neurons to the spinal cord.

Transmission: Signal is then transmitted to the dorsal root ganglia (cell body).

Perception: Signal reaches the brain, where it is interpreted as pain.

Pain Avoidance: Emotional reaction and withdrawal response are initiated.

Spinal cord: Central part of the nervous system for processing pain signals.
Transduction of Nociceptor Activators

Not all receptors are necessarily co-localized on the same cell membrane.
Pain Transmission Fibers

<table>
<thead>
<tr>
<th>Type</th>
<th>C-Polymodal Nociceptors</th>
<th>Ad Nociceptors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conduction</td>
<td>(0.5 - 2 m/sec)</td>
<td>(5 - 20 m/sec)</td>
</tr>
<tr>
<td>Modality</td>
<td>Thermal</td>
<td>High-Threshold</td>
</tr>
<tr>
<td></td>
<td>Pressure</td>
<td>Mechanoreceptors</td>
</tr>
<tr>
<td></td>
<td>Chemical</td>
<td>Pressure</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Thermal Pressure</td>
</tr>
</tbody>
</table>
Peripheral Nociceptors Do Not Adapt

- Sensitization of high-threshold mechanothermal nociceptor

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Spikes

Heat Stimuli

48 (°C)

35 (°C)
Peripheral Nociceptors Do Not Adapt

Nociceptor

Stimulus

Non-nociceptive thermoreceptor

Magnitude of afferent response

0

Temperature (°C)

40 45 50

Nociceptor

Thermoreceptor
Injury-Induces Changes in Pain Detection and Sensation

- **Secondary Hyperalgesia** (Central Sensitization)
- **Nerve Block**
  - No secondary hyperalgesia
- **Primary Hyperalgesia** (Peripheral Sensitization)

**Stimulus intensity vs. Response**

- **Hyperalgesia**: an increased response to a normally painful stimulus
- **Allodynia**: a painful response to a normally innocuous stimulus

**Subjective Pain Intensity**

- **Stimulus temperature (°C)**: 41, 43, 45, 47, 49
- **Pre-injury**
- **Post-injury**

**Graphs**

- **Response**
- **Stimulus intensity**
- **Pain threshold**
Peripheral Nociceptor Sensitization and Neurogenic Inflammation

- **Calor**: vasodilation --> heat

- **Rubor**: vasodilation --> redness

- **Tumor**: plasma extravasation --> swelling

- **Dolor**: activation of peripheral and adjacent nociceptors

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**Direct activation of nociceptor**

**Sensitization of nociceptor**

**Chemicals produced only during tissue injury**
# Chemical Mediators in Nociceptive Transmission

<table>
<thead>
<tr>
<th>Substance</th>
<th>Source</th>
<th>Pain in Man</th>
<th>Effect on Primary Afferents</th>
</tr>
</thead>
<tbody>
<tr>
<td>Potassium</td>
<td>Damaged Cells</td>
<td>++</td>
<td>Activate</td>
</tr>
<tr>
<td>Serotonin</td>
<td>Platelets</td>
<td>++</td>
<td>Activate</td>
</tr>
<tr>
<td>Bradykinin</td>
<td>Plasma Kininogen</td>
<td>+++</td>
<td>Activate</td>
</tr>
<tr>
<td>Histamine</td>
<td>Mast Cells</td>
<td>+</td>
<td>Activate</td>
</tr>
<tr>
<td>Prostaglandins</td>
<td>Damaged Cells</td>
<td>-</td>
<td>Sensitize</td>
</tr>
<tr>
<td>Leukotrienes</td>
<td>Damaged Cells</td>
<td>-</td>
<td>Sensitize</td>
</tr>
<tr>
<td>Substance P</td>
<td>Primary Afferents</td>
<td>-</td>
<td>Sensitize</td>
</tr>
</tbody>
</table>
Human Brain Imaging of Heat Pain

- Somatosensory Cortex
- Anterior Cingulate Cortex
- Insular Cortex
- Thalamus
- Spinomesencephalic Tract
- Spinoreticular Tract
- Anterolateral System
- Injury
- Primary Afferent Nociceptors
- Thalamus
- Anterior Cingulate Cortex
- Insular Cortex
- Prefrontal Cortex
Windup Induced by Repetitive C-Fiber Stimulation

- Persistent Nociceptive Input Changes Responses of 2nd Order Cells in the Spinal Dorsal Horn
Mechanisms of Central Sensitization

Presynaptically:
- Repetitive C-fiber input
- Increased transmitter release

Postsynaptically:
- Increased response to transmitter
- Strengthening of "synaptic efficacy"
Gate Theory of Pain

Ab Low Threshold Mechanoreceptor

Inhibitory Interneuron (e.g., GABA?)

C/Ad Nociceptor

2nd Order Pain Transmission Cell To Thalamus
Transcutaneous Electrical Nerve Stimulation

QuickTime™ and a TIFF (Uncompressed) decompressor are needed to see this picture.
Spinal Cord

Reticular Formation

Medial Thalamus

Lateral Thalamus

Somatosensory Cortex

Association Cortex

Sensation

Affect

Spinothalamic Tracts

Paleospinothalamic

Neospinothalamic
Endogenous Opioids Regulate Nociception

Spinothalamic Projection to Thalamus

Increased Enkephalin Release

Decreased Neurotransmission

Activation of Opioid Receptors:
- Decrease Ca$^{++}$ Conductance
- Increase K$^{+}$ efflux

Normal release of glutamate, substance P etc. promotes the transmission of pain

ENK

Nociceptive Input
Supraspinal Analgesia

- Brainstem circuits may inhibit rostral movement of nociceptive information and activate descending pathways that alter nociceptive processing in the spinal cord
  - periaqueductal gray
  - rostral ventral medulla
- Parts of the limbic system activated by opioids may alter the emotional response to painful stimuli
  - nucleus accumbens/ventral forebrain
Modulation of Pain: Serotonin and Norepinephrine

- DLPT: Dorsolateral Pontine Tegmentum (NE)
- RVM: Rostroventral Medulla (5-HT)

Visceral Pain

Anatomical
- mucosa
- muscle
- Serosa/mesentery

Functional
- mechanoreceptors
- chemoreceptors
- thermoreceptors
- nociceptors?
- polymodal

QuickTime™ and a TIFF (Uncompressed) decompressor are needed to see this picture.
Figure 41-1 These drawings representing the anterior (A) and posterior (B) views of the body illustrate areas to which various organs refer pain.
Reflex Somatic Theory

- Noxious stimulus
- Sensory pathway
- Motor pathway
- Spinal cord
- Pain
Clinical Features of Neuropathic Pain

- Pain occurs in the absence of a detectable ongoing tissue-damaging process;
- Abnormal or unfamiliar unpleasant sensations (dysesthesiae), frequently having a burning and/or electrical quality;
- Delay in onset after precipitating injury;
- Pain is felt in a region of sensory deficit;
- Shooting or stabbing component;
- Normally non-noxious stimuli are painful (allodynia);
- Pronounced summation and after-reaction to noxious stimuli (hyperalgesia).
Radiation Therapy Injury of Brachial Plexus

Abnormal Pain

Radiation Burn
Nerve Injury Induced Pain

Normal

Avulsion
Rhizotomy

Peripheral
Lesion
Injury Induced Changes in the Spinal Cord

Peripheral Injury
- Upregulate Growth-associated Proteins
  - Regenerative Capacity
  - Formation of Novel Inappropriate Synapses

Cell Death & Transganglionic Degeneration
- Vacant Synapses

Reorganization Of Spinal Circuits
Antihyperalgesic and/or Antiallodynic Agents Do Not Necessarily Produce Analgesia
## Neuropathic Cancer Pain

<table>
<thead>
<tr>
<th>Deafferentation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Symptoms</strong></td>
</tr>
<tr>
<td>Burning, shooting, stabbing, paroxysms, vicelike, electric shock</td>
</tr>
<tr>
<td>Injury to peripheral and/or CNS,</td>
</tr>
<tr>
<td><strong>Causes</strong></td>
</tr>
<tr>
<td>from tumor infiltration or cancer therapy</td>
</tr>
<tr>
<td><strong>Examples</strong></td>
</tr>
<tr>
<td>Metastatic or radiation-induced</td>
</tr>
<tr>
<td>brachial or lumbosacral plexopathies;</td>
</tr>
<tr>
<td>spinal cord compression, postherpetic neuralgia</td>
</tr>
</tbody>
</table>
**Scope of the Problem**

- **Patients with pain:**
  - at least 50% of all cancer patients
  - more than 70% of patients with advanced cancer

- **Pain intensity:**
  - moderate to severe in approximately 50% of patients with pain
  - excruciating in 30% of patients with pain

50% TO 80% OF CANCER PATIENTS DO NOT OBTAIN SATISFACTORY PAIN RELIEF

(Bonice, 1985; WHO, 1986)
## Pain Management Techniques

<table>
<thead>
<tr>
<th>Pharmacotherapy</th>
<th>Non-Pharmacological Treatments</th>
<th>Physical therapy</th>
<th>Procedures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Opioids</td>
<td>Acupuncture</td>
<td>Active exercise</td>
<td>Trigger point injections</td>
</tr>
<tr>
<td>Nonsteroidals</td>
<td>Relaxation</td>
<td>Passive exercises</td>
<td>Nerve blocks</td>
</tr>
<tr>
<td>Muscle relaxants</td>
<td>Visualization</td>
<td>Pool therapy</td>
<td>Epidural steroids</td>
</tr>
<tr>
<td>Benzodiazepines</td>
<td>Prayer</td>
<td>TENS unit</td>
<td>Intrathecal opioids</td>
</tr>
<tr>
<td>Antidepressants</td>
<td>Pain groups</td>
<td>Massage therapy</td>
<td>Spinal cord stimulation</td>
</tr>
<tr>
<td>Antianxiety agents</td>
<td></td>
<td>Chiropractic</td>
<td></td>
</tr>
<tr>
<td>Antiarrhythmics</td>
<td></td>
<td>Ice/heat</td>
<td></td>
</tr>
<tr>
<td>Antiseizure agents</td>
<td></td>
<td>Bed rest</td>
<td></td>
</tr>
</tbody>
</table>
Pain Assessment

• Pain is a highly variable sensation that has both sensory and affective components
  - Great individual variability

• There is a key difference between statistical significance and clinical significance when it comes to analgesia

• A reduction in pain levels should not be equated to sufficient pain relief
  - Some patients may not be seeking complete pain relief; side-effects may limit the maximum tolerated dose
Assessment of pain in humans is unique in that patients can typically verbalize both the intensity and quality of the pain, and how it is impacting their quality of life.

There are a number of inventories that have been used to evaluate pain in humans:

- Single-dimension self-report measures
- McGill Pain Questionnaire (MPQ)
- Brief Pain Inventory (BPI)
- West-Haven-Yale Multidimensional Pain Inventory (WHYMPI)
Visual Analog Scales

- Used as self-report scales of pain intensity
- Simple and efficient to administer
- Effective for several patient populations because scaling is not limited to words

Rate Pain Intensity

Visual Analog Scale (VAS)

No Pain  |  0  |  1  |  2  |  3  |  4  |  5  |  6  |  7  |  8  |  9  |  10  | Worst Possible Pain
---|---|---|---|---|---|---|---|---|---|---|---|---
No Hurt | 0  | 1  | 2  | 3  | 4  | 5  | 6  | 7  | 8  | 9  | 10  | No Pain

McGill Pain Questionnaire

- Used to quantify a patient’s pain experience
- Consists of a series of 102 pain descriptors that are grouped into three dimensions of pain: sensory, affective, and evaluative
- Takes about 5 minutes to complete

Talk to Patients About Their Pain
Pain Assessment Questions to Ask

- Talk to your Patients about their Pain
  - Where is the pain located?
  - What does it feel like (sharp, dull, burning)?
  - When did it begin? How long does it last?
  - What makes it better? What makes it worse?

- Rate Pain Intensity
  - What is your level of pain most of the time? (0-10 scale)?
  - When is your pain the worst/best?
  - What is your pain level when you rest? During movement?

- Evaluate Limitations on Activities
  - What daily activities do you avoid because of pain?
  - Does pain interfere with your ability to sleep/walk/work/play?
  - How does pain affect your mood and relationships?
Evaluate Limitations on Activities

- Fully active without restriction
- Activity restricted; ambulatory; “light” work only
- Ambulatory; all self-care; no work activities; up > 50% waking hours
- Limited self-care; confined > 50% waking hours
- Completely disabled

www.painfoundation.org
Pain is often associated with other emotions that can exacerbate the situation
- Anxiety, loss of control, etc.

Interventions should be initiated that minimize these emotions
- Involving the patient in the overall plan (e.g., PCA)
- Nonpharmacological strategies including reassurance, distraction, etc.
- Use of adjunct agents including anxiolytics, antidepressants, etc.
Additional Analgesia Options

• Use nonpharmaceutical treatments to reduce pain
  - Distraction, hypnosis, etc.
  - Encouraging the patient to use techniques that have worked for them

• Use of nitrous oxide or fentanyl for setting fractures
  - No need for the “this will only hurt for a minute”

• Regional anesthesia in elderly patients to eliminate the cognitive effects of opioids and other CNS acting agents
Principles of Pain Control

1. Analgesia should be integrated into a comprehensive patient evaluation and management plan
2. The emotional and cognitive aspects of pain must be recognized and treated
3. There is no reliable way to objectively measure pain
4. Pain is most often under-treated, not over-treated
5. Beware of the “squeaky-wheel-gets-the-oil” phenomenon of pain control
6. Pain control must be individualized
7. Anticipate rather than react to pain
8. Whenever possible, let the patient control his or her own pain
9. Pain control is often best achieved by combination therapy
10. Pain control requires a multidisciplinary team approach