Pain Society of the Carolinas 2015: Nerve Injury and Neuropathy

Thomas Buchheit, MD
Associate Professor
Director of Pain Medicine
Department of Anesthesiology
Duke University Medical Center
Durham VAMC
Disclosures

• Consulting:
  – Bioventus
  – DARA Bioscience
  – Thar Pharmaceuticals

• Research funding:
  – Department of Defense: CDMRP DM102142
Outline

• Anatomy and imaging
• Physiology of nerve injury
• Current Therapies
• Future directions
Anatomy: Types of Nerve Injury
The Endoneural Environment

• Regulation occurs within the perineurium
  – Relatively impermeable
  – Sensitive to intrafascicular injection
  – Permeability altered by Schwann cell, macrophage and mast cell activity

• Neuropathies can be considered perturbations of endoneurial homeostasis

Nerve Response to Injury

Stewart: Focal Peripheral Neuropathies
2nd, Ed.'93, Praven press
Degrees of Injury

• **Neurapraxia**: Temporary nerve dysfunction
  – Most patients will see recovery within 3 months or less

• **Axonotmesis**:
  – Wallerian degeneration
    • Axonal and myelin degeneration distal to point of injury
  – Preserved epineurium and basal lamina

• **Neurotmesis**:
  – Complete division of a peripheral nerve and connective tissue structures
    • Will not regenerate along original channels
    • May form neuroma at transection site
Compression Neuropathies: Peripheral Nerve
EMG Findings in CTS

- Most common compressive mononeuropathy (1-5% of population)
- Edema and thickening of vessel walls in the endoneurium
- Myelin thinning and fibrosis seen
  - Motor nerve conduction slow
  - Sensory fibers more sensitive to compression than motor fibers
- Axon loss can be seen in advanced cases
Compression Neuropathies:
Proximal Nerve/DRG
Transection Neuromas
Post Amputation Phenotype Adjudication

Phantom Pain

Residual Limb Pain

Somatic

Neuropathic

Neuroma

CRPS

Mosaic Neuralgia

Figure 1. Phenotype Adjudication Algorithm

CRPS Budapest Clinical Criteria: Symptoms in ¾ of the following categories: Sensory (hyperalgesia or allodynia), Vascular (temperature, skin color), Sweating/Edema, and Motor (weakness, tremor dystonia)/Trophic (hair, skin).

Physical exam signs in 2/4 of the following categories: Sensory (alodynia), Vascular, Sweating/Edema, or Motor/Trophic.

S-LANSS score: Somatic pathology or S-Lanss <12, S-Lanns Score ≥ 12

Buchheit T, and Van de Ven T., Pain Phenotypes and Risk Factors Following Traumatic Amputation: Results from Veterans Integrated Pain Evaluation Research (VIPER)
## Pain Phenotype Results

### Pain Phenotypes

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>Total Patients Enrolled</th>
<th>All Patients n=124</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any Patient with Pain (NRS&gt;0)</td>
<td></td>
<td>Any Pain n=115 (92.7%)</td>
</tr>
<tr>
<td>Patients with Significant Pain (NRS≥3)</td>
<td></td>
<td>All Significant Pain n=80 (64.5%)</td>
</tr>
<tr>
<td>Residual Limb Pain (NRS≥3)</td>
<td></td>
<td>Significant Residual Limb Pain n=76 (61%)</td>
</tr>
<tr>
<td>Phantom Limb Pain (NRS≥3)</td>
<td></td>
<td>Significant Phantom Limb Pain n=72 (58%)</td>
</tr>
</tbody>
</table>

### Phenotypic Subtypes of Significant Residual Limb Pain

<table>
<thead>
<tr>
<th>Subtype</th>
<th>n (Percentage of Significant Residual Limb Pain)</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neuroma</td>
<td>37 (48.7%)</td>
<td>2 +35 Neuroma</td>
</tr>
<tr>
<td>Somatic</td>
<td>31 (40.8%)</td>
<td>4 +27 Somatic</td>
</tr>
<tr>
<td>CRPS</td>
<td>15 (19.7%)</td>
<td>CRPS n=15</td>
</tr>
<tr>
<td>Mosaic</td>
<td>8 (10.5%)</td>
<td>2 +6 Mos</td>
</tr>
</tbody>
</table>

Buchheit T, and Van de Ven T., Pain Phenotypes and Risk Factors Following Traumatic Amputation. Pain medicine 2015
Is Phantom Pain a Central or a Peripheral Problem?
Physiology of Nerve Injury
Neuroinflammatory Mechanisms

Neuroinflammatory Mechanisms

Von Hehn, Baron and Woolf: Deconstructing the neuropathic pain phenotype. Nature 2012
Neuroinflammatory Mechanisms in Disc Herniation

- TNF and other cytokines are released by Schwann cells at site of injury and DRG
- After peripheral nerve injury:
  - 25% of ectopic activity at peripheral axon
  - 75% at DRG
Inflammation-Driven Phenotypic Change

- Macrophage infiltration and cytokine release at site of axonal injury and DRG
  - Microglial activation
    - Microglia number increase by 2-4 fold in dorsal horn
  - Astrocyte activation persists for months

Neuroma Ectopic Activity

- Injury leads to:
  - Mechanical sensitivity
    - Focal demyelination of A-fibers at site of injury
  - Ectopic activity
    - Proliferation of Nav 1.7 and 1.8 channels at injury and DRG
  - Catecholamine sensitivity
    - Sympathetic sprouting at DRG

Neuroinflammatory Mechanisms in the Clinic
Common Immune-Associated Neuropathic Pain Syndromes

• Myelinopathies:
  – Autoimmune Neuropathies (Guillain-Barré)
  – Chronic inflammatory demyelinating polyneuropathy (CIDP)

• Multiple sclerosis

• CRPS
CRPS: Inflammatory Mechanism

- Serum concentrations of IL-6, and TNF-alpha are elevated
- Joint fluid demonstrates increased protein and neutrophils
- Cytokine inhibitors improve symptoms, especially in early warm CRPS
- Animal model of fracture/casting
  - Demonstrates inflammatory changes that do not occur in soft tissue injury
- Improved CRPS symptoms in patients treated with IVIG, DMARDs, and bisphosphonates

Neuroinflammation in non-CRPS Neuropathy

• Small fiber neuropathy:
  – Skin biopsy demonstrates increased gene expression of IL-1β, TNFα, IL-6, IL-8

Are there differences in systemic cytokine levels in patients with persistent pain after amputation?
Current Therapies

Neurolytic Therapies
Neurolytic Therapies for Neuroma and Nerve Injury Pain

- Radiofrequency Lesioning
- Cryoneurolysis
- Chemical Neurolysis
  - 2 observational trials demonstrating significant improvement in treatment of amputation neuromas

Prevention in an Amputation Injury Model
Preventive Analgesic in Amputation Injury

• Ketamine\(^1\):
  – No significant difference in the incidence of phantom pain at 6 months (47% phantom pain in ketamine and 71% in control group, \(p=0.28\))

• Gabapentin\(^2\):
  – No effect when started on POD #1 and continued 30 days at 2,400mg/d

• Memantine\(^3\):
  – No effect when 20mg/day memantine compared with placebo

Preventive Trials for Post-amputation Pain

• 2010 systematic review
  – 11 studies of epidural and perineural catheter use
    • Good evidence for efficacy in treating acute postoperative pain
    • No robust evidence that preventive techniques reduce the incidence of chronic pain

Preventive Trials: Is Duration of Therapy Important?

• Longer-term perineural catheter use:
  – Borghi 2010
    • Average catheter duration 30 days
    • 84% pain free at 12 months

## Risk Factors for Post-amputation Pain

The odds ratios for development of chronic pain (all types), neuropathic pain, phantom limb pain, all types of residual limb pain, somatic residual limb pain, residual limb pain from presence of neuroma, complex regional pain syndrome, mosaic neuropathic residual limb pain and all neuropathic residual limb pain are reported above with p-values in brackets. Factors associated with significant risk of a specific pain subtype (p-value < 0.050) are marked with an asterisk and italicized. The data presented in the final column include total patients with neuropathic pain regardless of case or control status.

### Table 4: Clinical risk factors for development of post-amputation chronic pain subtypes

<table>
<thead>
<tr>
<th>Clinical Factor</th>
<th>Chronic Pain (cases) OR (CI) [p value]</th>
<th>Phantom Pain (cases) OR (CI) [p value]</th>
<th>RLP (cases) OR (CI) [p value]</th>
<th>RLP-Somatic (cases) OR (CI) [p value]</th>
<th>RLP-Neuropathic (cases) OR (CI) [p value]</th>
<th>RLP-Neuroma (cases) OR (CI) [p value]</th>
<th>RLP-CRPS (cases) OR (CI) [p value]</th>
<th>RLP-Mosaic (cases) OR (CI) [p value]</th>
<th>Neuropathic Pain (All) OR (CI) [p value]</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCS</td>
<td>13.39 (1.73-103.87) [0.0016]*</td>
<td>6.20 (0.34-112.49) [0.1876]</td>
<td>3.05 (0.16-59.29) [0.194]</td>
<td>0.48 (0.15-1.50) [0.0735]</td>
<td>2.71 (0.87-8.45) [0.0899]</td>
<td>2.47 (0.85-7.14) [0.3474]</td>
<td>1.82 (0.53-6.20) [1.0000]</td>
<td>1.08 (0.20-5.85) [1.0000]</td>
<td>3.78 (1.28-11.18) [0.0103]*</td>
</tr>
<tr>
<td>PTSD-M</td>
<td>10.08 (1.28-79.14) [0.0099]*</td>
<td>1.72 (0.20-15.14) [1.0000]</td>
<td>2.31 (0.12-45.15) [1.0000]</td>
<td>0.19 (0.04-0.89) [0.0373]*</td>
<td>6.92 (1.44-33.17) [0.0008]*</td>
<td>6.67 (1.71-26.04) [0.0003]*</td>
<td>7.13 (1.98-25.70) [1.0000]</td>
<td>0.58 (0.07-5.12) [1.0000]</td>
<td>9.28 (2.01-42.88) [0.0010]*</td>
</tr>
<tr>
<td>PHQ-9</td>
<td>2.40 (0.94-6.13) [0.055]</td>
<td>9.13 (0.51-164.62) [0.0520]</td>
<td>4.46 (0.23-86.00) [0.0306]</td>
<td>0.38 (0.13-1.09) [0.0624]</td>
<td>3.53 (1.22-10.19) [0.0142]*</td>
<td>3.72 (1.36-10.15) [0.0006]*</td>
<td>4.59 (1.42-14.91) [1.0000]</td>
<td>0.71 (0.13-3.79) [1.0000]</td>
<td>4.46 (1.81-10.99) [0.0006]*</td>
</tr>
<tr>
<td>Regional Catheter</td>
<td>0.63 (0.30-1.33) [0.227]</td>
<td>5.00 (0.58-42.80) [0.142]</td>
<td>1.96 (0.19-19.70) [1.0000]</td>
<td>1.24 (0.50-3.12) [0.6423]</td>
<td>0.91 (0.37-2.25) [0.8397]</td>
<td>1.42 (0.58-3.51) [0.4443]</td>
<td>2.09 (0.67-6.49) [0.2034]</td>
<td>0.20 (0.02-1.71) [0.142]</td>
<td>0.44 (0.21-0.92) [0.0269]*</td>
</tr>
</tbody>
</table>
Incidences of Chronic Pain with Regional Catheter Post-Injury
Future directions
We can’t (and shouldn’t?) prevent inflammation after injury.

Can we facilitate recovery and resolution?
Future Treatments

- Immune modulation
  - IVIG
  - Bisphosphonates
  - Cytokine inhibitors
    - Positive pilot data for etanercept use for neuromas

- Epigenetic intervention

- Novel pathway discovery
  - Wnt, NOD

Why aren’t we treating the inflammatory component of CRPS routinely?
Intravenous Immunoglobulin Treatment of the Complex Regional Pain Syndrome
A Randomized Trial
Andreas Goebel, MD, PhD; Andrew Baranowski, MD; Konrad Maurer, MD; Artemis Ghiai, RGN; Candy McCabe, PhD; and Gareth Ambler, PhD

Figure 2. Mean pain intensity for each day after the infusion.
Role of Alendronate in Therapy for Posttraumatic Complex Regional Pain Syndrome Type I of the Lower Extremity

Daniel-Henri Manicourt, Jean-Pierre Brasseur, Yves Boutsen, Geneviève Depreux, and Jean-Pierre Devogeleer
Treatment of complex regional pain syndrome type I with neridronate: a randomized, double-blind, placebo-controlled study

Massimo Varenna¹, Silvano Adami², Maurizio Rossini², Davide Gatti², Luca Idolazzi², Francesca Zucchi¹, Nazzarena Malavolta³ and Luigi Sinigaglia¹
What causes these inflammatory and expression changes after injury?

Epigenetic Modifications
Can we alter gene expression?

<table>
<thead>
<tr>
<th>Epigenetics Mechanism</th>
<th>Drug</th>
<th>Action</th>
<th>Clinical Use</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Histone Deacetylase Inhibitor</td>
<td>Valproic Acid</td>
<td>Inhibits Class I and II HDAC</td>
<td>Seizures, Pain</td>
<td>Effective for migraine prophylaxis</td>
</tr>
<tr>
<td></td>
<td>Givinostat</td>
<td>Inhibits Class I and II HDAC</td>
<td>Juvenile idiopathic arthritis</td>
<td>Effective in human arthritis trial</td>
</tr>
<tr>
<td></td>
<td>Tricostatin A (TSA)</td>
<td>Inhibits Class I and II HDAC</td>
<td>Laboratory only</td>
<td>Produces analgesia in animal models.</td>
</tr>
<tr>
<td></td>
<td>Suberoylanilide hydroxamic acid (SAHA)</td>
<td>Inhibits Class I HDAC</td>
<td>Laboratory only</td>
<td>Produces analgesia in animal models.</td>
</tr>
<tr>
<td>DNA Methylation</td>
<td>Glucosamine</td>
<td>Prevents demethylation of IL-1β gene promoter</td>
<td>Arthritis pain</td>
<td>Common clinical use. Effect on IL-1β reduces inflammatory cytokine production</td>
</tr>
<tr>
<td></td>
<td>Valproic Acid</td>
<td>Induces demethylation of Reelin promoter</td>
<td>Seizures, Pain</td>
<td>Reelin modulates NMDA function and pain processing</td>
</tr>
<tr>
<td></td>
<td>L-methionine</td>
<td>Induces methylation at glucocorticoid receptor promoter gene</td>
<td>Dietary Supplement</td>
<td>Alters experimental stress response. Used as dietary supplement for arthritis</td>
</tr>
<tr>
<td>RNA interference</td>
<td>siRNA targeted to NMDA receptor subunits</td>
<td>Gene silencing of NR1 and NR2 subunits of NMDA</td>
<td>Experimental</td>
<td>Produces analgesia in animal models</td>
</tr>
<tr>
<td></td>
<td>siRNA to P2X3</td>
<td>Gene silencing of P2X3</td>
<td>Experimental</td>
<td>Produces analgesia in animal models. No observed neurotoxicity with intrathecal use</td>
</tr>
<tr>
<td></td>
<td>siRNA to TNF-α</td>
<td>Gene silencing of TNF-α</td>
<td>Experimental</td>
<td>Produces analgesia in animal models</td>
</tr>
</tbody>
</table>
Conclusions

- Proper diagnosis (better phenotyping) is a precursor to improving therapies
- Neuroinflammation is a part of most neural injury pain states regardless of injury site
- Preventive techniques may be effective with longer duration of therapy
- “Next generation” therapies will likely include immune modulation and epigenetic intervention