Managing Neuropathic Pain in Children with Cancer

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Objectives

• Overview of pain in children with cancer
• Define nociceptive and neuropathic pain (NeP)
• Outline prevalence of NeP in childhood cancer
• Describe steps in comprehensive assessment of NeP
• Outline treatment recommendations for NeP
• Future research
What is Pain?
What is Pain?

• “An unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage”
  
  (IASP, 1979)

• Pain is “whatever the experiencing person says it is, existing whenever the experiencing person says it does”
  
  (McCaffery & Beebe, 1989)
The Problem

• Most children with cancer experience acute pain (due to disease, invasive procedures and treatment toxicities) as well as chronic pain

• Pain is a common across all types of childhood cancers and can negatively affect quality of life
Case Study - PJ

• 13 year old male with ALL
• ALL initiation treatment: intrathecal methotrexate, Vincristine, Prednisone + others
• Numbness and tingling in hands and feet, chest pain and HA
• “feels like my skin is on fire from the neck down”, “like fireworks coming out of my chest”, at times “like an earthquake with aftershocks”.
• Pain intensity rated at 12-13/10 on Verbal NRS
• Impaired sleep and PTSD
ACUTE VERSUS CHRONIC PAIN: WHAT ARE THE DIFFERENCES?
Question

Which of the following statements about chronic pain is FALSE?

A. Serves no protective function
B. Usually has a single obvious cause
C. Lasts beyond the time of normal healing
D. Pain intensity is often out of proportion to objective finding
Classification of pain

Pain

- Pain classified by duration
  - Acute
  - Chronic

- Pain classified by nature
  - Nociceptive
    - Somatic
    - Visceral
  - Non-nociceptive
    - Neuropathic
    - Sympathetic
What is Chronic Pain?

• Chronic pain is a term used to describe persistent or recurrent pain.

• Chronic pain in children and adolescents is commonly defined as any prolonged pain that lasts longer than expected healing time (arbitrarily defined as > 3 months), or any recurrent pain that occurs at least three times throughout a period of three months (APS, 2012).
<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Acute Pain</th>
<th>Chronic Pain</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cause</strong></td>
<td>Usually single obvious cause (e.g. tissue damage due to surgery)</td>
<td>Usually multiple causative or triggering factors Neuronal or CNS abnormality (plasticity, sensitization)</td>
</tr>
<tr>
<td><strong>Type</strong></td>
<td>Nociceptive and or neuropathic</td>
<td>Nociceptive, neuropathic or mixed; psychosocial factors</td>
</tr>
<tr>
<td><strong>Purpose</strong></td>
<td>Protective; activation of sympathetic nervous system</td>
<td>No protective function; rarely accompanied by signs of activation of sympathetic nervous system</td>
</tr>
<tr>
<td><strong>Duration</strong></td>
<td>Short-lived (days to weeks)</td>
<td>Long lasting or recurring beyond time of normal healing, may be associated with chronic disease</td>
</tr>
<tr>
<td><strong>Pain Intensity</strong></td>
<td>Usually proportionate to severity of injury</td>
<td>Often out of proportion to objective physical findings</td>
</tr>
<tr>
<td><strong>Treatment</strong></td>
<td>Usually easy to treat with single modalities (pharmacological or physical)</td>
<td>More difficult to treat, requiring multidisciplinary, multi-modal treatment approach</td>
</tr>
<tr>
<td><strong>Outcome</strong></td>
<td>Expected to resolve with healing</td>
<td>Pain persists in significant proportion (30-62%); with smaller proportion developing pain associated disability syndrome (5-8%)</td>
</tr>
</tbody>
</table>
Pain Continuum

- It is now postulated that acute and persistent or chronic pain are a continuum, rather than separate entities, for example, in some situations neuropathic pain may be a component of acute pain, that is, due to postoperative pain, cancer pain or trauma.

(Australian and New Zealand College of Anaesthetists and Faculty of Pain Medicine [ANZCA] 2005).
<table>
<thead>
<tr>
<th>Nociceptive</th>
<th>Neuropathic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ordinary pain sensation</td>
<td>Arises from nervous system itself (nerve injury or disease)</td>
</tr>
<tr>
<td>that arises from injury or</td>
<td></td>
</tr>
<tr>
<td>damage to some part of the</td>
<td>Described as a burning or shooting sensation</td>
</tr>
<tr>
<td>body other than the nerve tissue itself</td>
<td></td>
</tr>
<tr>
<td>Usually sharp or aching and</td>
<td>Can lead to a heightened sensitivity to stimuli (i.e., gentle touch is interpreted as painful)</td>
</tr>
<tr>
<td>well localized</td>
<td></td>
</tr>
<tr>
<td>Usually responsive to non-</td>
<td>Tends to be more difficult to treat</td>
</tr>
<tr>
<td>opioids and/or opioids</td>
<td></td>
</tr>
<tr>
<td>Somatic (bone, muscle, joint,</td>
<td>Treatment usually includes adjuvant analgesics</td>
</tr>
<tr>
<td>skin or connective tissue)</td>
<td></td>
</tr>
<tr>
<td>Visceral – organs such as</td>
<td>Phantom limb pain, peripheral neuropathies due to nerve compression or entrapment</td>
</tr>
<tr>
<td>stomach and pancreas</td>
<td></td>
</tr>
</tbody>
</table>
Causes of NeP in Cancer

• Tumor invasion/compression of nerves
• Nervous system tumour (i.e., neurofibromatosis)
• Post-surgical -> limp-sparing surgery (i.e, rotationplasty), amputation (phantom limb pain)
• Effect of treatment -> chemotherapy, radiation therapy
• Hematopoietic stem cell transplantation
WHAT DO WE KNOW ABOUT NEUROPATHIC PAIN IN CHILDREN WITH CANCER?
Prevalence of NeP in ALL

• Retrospective study to identify risk factors, incidence and use of therapeutic and prophylactic gabapentin in NeP in ALL (St. Jude’s)
• Dose limiting SE involves both autonomic and sensorimotor neuropathy -> NeP
• 498 patients treated on single protocol for ALL
• 34.9% (174/498) had 207 episodes of NeP
• Most common sites: lower extremity, back and jaw
• 16% (28/174) had at least one recurrence of NeP

Anghelescu et al., Ped Blood Cancer, 2011
Predictors of NeP in ALL

• White non-Hispanic race only predictive variable (higher incidence CYP3A5*3 allele)
• Incidence in 1-5 yr olds 30.6% vs 40% for 16-20 year olds (may reflect developmental differences in ability to dx NeP)
• No difference between severity of NeP and cumulative dose of vincristine or dose of vincristine immediately preceding the dx

Anghelescu et al., Ped Blood Cancer, 2011
 Gabapentin with NeP in ALL

- 62.2% (112) and 37.8 % (68) were Rx with gabapentin or opioids respectively
- Selection of gabapentin or opioids was not influenced by the pain intensity score at time of dx of NP
- 81% did not have a recurrence after treatment with gabapentin and most had improved pain scores
- Found no evidence that gabapentin prevented recurrence of NeP

Anghelescu et al., Ped Blood Cancer, 2011
NeP Referrals to Pediatric Cancer Pain Service

• Retrospective review from a 3.5 year period
• 15% (66/439) of referrals were for NeP
• 1401 (55.5%) inpatient visits and 623 (44.5%) outpatient visits
• NeP patients had significantly greater mean number of pain visits per consultation (p= 0.008) and significantly more days (median) of pain service follow-up (<0.001) than other patients
• Most common cause of NeP was cancer treatment rather than underlying malignancy

Anghelescu et al., Pain Management Nsg, 2014
More about Referrals

• NeP is less frequent than non-NeP in children with cancer
• It was more difficult to treat and required longer follow-up (more clinical visits)
• Required complex pharmacological (average 3 medications) and non-pharmacological interventions

Anghelescu et al., Pain Management Nsg, 2014
Patient Characteristics with NeP

- Most common descriptors: burning, shooting, tingling, needles and pins
- Majority of NeP – solid tumor (37/56; 66.1%) and most were osteosarcoma (24/37), followed by limb sparing and chemotherapy
- Pharmacological Rx: 97% opioid; 90.9% anticonvulsants; 58/66 received combination (87.9%); 24/66 Rx amitriptyline
- Nonpharm (psych and physical) – 38/66 (57.6%)

Anghelescu et al., Pain Management Nurs, 2014
ASSESSING NEUROPATHIC PAIN
When evaluating a child’s neuropathic pain, which of the following is most important to assess?

A. Pain characteristics
B. Level of functional impairment
C. Psychological contributors
D. Current and past pain control strategies
E. All of the above
Clinical Diagnosis of NeP

• Clinical history is mainstay of dx in children
• Word descriptors - burning, shooting, shock like
• Intensity, quality, temporal aspects of pain, response to treatment
• Physical exam: verify and locate lesion of somatosensory system and associated neurological signs
• Assessment of pain-related disability
• Quantitative sensory testing (QST) - assessing sensory function with graded stimuli
Terminology Associated with NeP

- **Allodynia**: Severe pain triggered by innocuous (non-harmful) stimuli such as stroking, the touch of clothing on the affected area, or changes in temperature.
- **Dyesthessia**: An unpleasant abnormal sensation, which may be spontaneous or evoked (e.g., shooting, tingling sensations).
- **Hyperalgesia**: A reduced threshold to pain.
- **Hyperpathia**: Increased pain from stimuli which are normally painful (e.g., increased sharpness from a pin prick).
- **Paresthesia**: An abnormal sensation, which may be spontaneous or evoked (e.g., pins and needles).
Goals of Pain Assessment

• Describe the pain and factors that influence it
• Assists in the diagnosis of chronic pain problem and development of appropriate pain management plan (guides choice of pain treatment strategies)
• Evaluate the effectiveness of those interventions
Comprehensive Pain Assessment

• Comprehensive assessment includes:
  ✓ A detailed pain history
  ✓ Conduct medical examination and appropriate diagnostic tests
  ✓ Evaluate probable involvement of nociceptive and neuropathic mechanisms
  ✓ Appraisal of situational factors contributing to a child’s pain

• Ongoing reassessment of pain
Bio-psycho-social Model

- **Psychological Factors**
  - Temperament
  - Anxiety & Mood
  - Coping Style
  - Family and child beliefs about pain

- **Environmental Factors**
  - Family
  - School
  - Peers

- **Child Factors**
  - Age
  - Gender
  - Cognitive Level
  - Culture

- **Level of Disability**
  - Sleep
  - School
  - Social
  - Physical

- **Physiological**
  - General Health
  - Pain Characteristics
  - Hormone Levels
  - Injury
Sensory Characteristics

- **Location**: “Where do you hurt?”
- **Intensity**: “How much does it hurt?” (using valid tools)
- **Quality**: “What does it feel like?”
- **Duration**: “How long does it last?”
- **Frequency**: “How often does it come?”
- **Accompanying symptoms**: “What else do you feel?”
- **Seasonal/temporal variation**: “When does it come?”
- **Alleviating / Aggravating factors**: “What makes the pain better/worse?”
How has pain impacted the child’s life?

- Pain Related Disability
  - Sleep
  - Mood
  - School/role function
  - Social
  - Physical
  - Relationships (peers, family)
More about Assessment...

Psychological Factors

✓ What stressors may be aggravating the pain?
✓ Fear of pain and movement
✓ Frustration, sadness and worry regarding pain and impact of pain on life?
✓ Child and parent beliefs about pain, perceived cause and prognosis?
✓ Underlying psychological factors (anxiety disorder, mood disorder, post-traumatic stress)?
### Past/current pain control methods and their effectiveness

- **Pharmacological**
  - OTC drugs
  - Neuropathic pain meds
  - Opioids

- **Physical**
  - Physiotherapy
  - Massage / Acupuncture
  - Cold / Heat

- **Psychological**
  - Relaxation
  - Distraction
  - Psychological therapy

- **Complementary and Alternative Medicines**
  - Herbal
  - Traditional Remedies
NeP Assessment tools

• Validated tools in adults
  – *Douleur Neuropathique en 4 Questions* (DN4): seven interview questions and three physical tests
  – *Leeds Assessment of Neuropathic Symptoms and Signs* (LANSS): five interview questions and two physical tests

• None have been validated in pediatrics
Pain Squad: PJ Pain data
<table>
<thead>
<tr>
<th>Activity of Daily Living</th>
<th>Interference (/10; M ± SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sleep</td>
<td>3.7 ± 2.6</td>
</tr>
<tr>
<td>Being active</td>
<td>4.3 ± 2.4</td>
</tr>
<tr>
<td>Emotions</td>
<td>5.7 ± 2.0</td>
</tr>
<tr>
<td>Walking</td>
<td>3.6 ± 2.2</td>
</tr>
<tr>
<td>Relationships</td>
<td>3.2 ± 1.7</td>
</tr>
<tr>
<td>Schooling</td>
<td>1.3 ± 2.7</td>
</tr>
<tr>
<td>Enjoying life</td>
<td>5.1 ± 2.0</td>
</tr>
</tbody>
</table>
MANAGEMENT OF NEUROPATHIC PAIN: 3P’S
Question

When treating a child’s neuropathic pain, which of the following is true?

A. Best treated with medications alone
B. Usually responds to one modality
C. Psychological strategies are not effective for NeP
D. Multimodal and biopsychosocial approach is most effective in treating NeP
E. None of the above
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B. Usually responds to one modality
C. Psychological strategies are not effective for NeP
D. Multimodal and biopsychosocial approach is most effective in treating NeP
E. None of the above
Goals of Treatment

• The management of chronic pain involves the use of a range of psychological, physical and pharmacological interventions (The 3 Ps)

• Decisions regarding the most appropriate treatments should be individualized and based on the assessment

• Interventions should be aimed at treating any trigger factors, as well as the underlying cause(s) of the pain

• Referral to a multidisciplinary paediatric pain program should be considered for children with complex or ongoing chronic NeP pain
## Overview of Treatments

<table>
<thead>
<tr>
<th>Pharmacological Interventions</th>
<th>Physical Interventions</th>
<th>Psychological Interventions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Simple analgesics</td>
<td>Exercise</td>
<td>Education (about pain experience and pain problem)</td>
</tr>
<tr>
<td>Opioid analgesics</td>
<td>Thermal stimulation (heat, cold, desensitisation)</td>
<td>Sleep hygiene</td>
</tr>
<tr>
<td>Anticonvulsants</td>
<td>Physiotherapy</td>
<td>Relaxation</td>
</tr>
<tr>
<td>Antidepressants</td>
<td>Occupational therapy</td>
<td>Biofeedback</td>
</tr>
<tr>
<td>Antiarrhythmics (alpha-</td>
<td>Massage</td>
<td>Behavioural therapies</td>
</tr>
<tr>
<td>adrenergic blockers)</td>
<td>TENS</td>
<td>Cognitive therapies</td>
</tr>
<tr>
<td>Anxiolytics</td>
<td>Acupuncture</td>
<td>Cognitive behavioural therapy (CBT)</td>
</tr>
<tr>
<td>Nerve blocks</td>
<td></td>
<td>Acceptance and commitment therapy (ACT)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mindfulness therapy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Family therapies</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Psychotherapy</td>
</tr>
</tbody>
</table>
Pharmacology: Key Principles

• Multimodal + biopsychosocial approach
• Balanced analgesia (opioids and TCA/gabapentionoids)
• Tricyclic antidepressants (amitriptyline) and gabapentionoids/pregabalin (can take 4-6 weeks)
• Topical if localized (5% lidocaine)
• Consider regional blocks
Role of Physical Therapies

- Chronic pain often leads children to avoid physical activities due to fear of re-injury or because it exacerbates the pain (called kinesiophobia).
- Lack of use leads to loss of muscle strength, flexibility, endurance and overall de-conditioning.
- Desensitization exercises (allodynia).
- Regular exercise (20 minutes three times per week) can also help improve sleep, mood, self-esteem and energy levels. (McCarthy et al. 2003; Engel and O’Rourke 2006; Stinson 2006).
There are many psychological therapies available to treat chronic pain in children.

Often these therapies are integrated into a comprehensive cognitive-behavioural therapy (CBT) program that is directed at identifying and ameliorating trigger factors that affect the child’s pain and disability.

Mindfulness and acceptance based therapies.
Cognitive Behavioral Therapies

Such programs usually include:

- Education about the pain
- Learning cognitive behavioural pain coping skills (for example, imagery, distraction and relaxation)
- Stress management (for example, identifying and coping with stressful situations, using thought stopping, cognitive restructuring, assertiveness and problem solving)
- Relapse prevention
- Evidence for acute and chronic pain; minimal research in NeP in children *(Palermo et al., 2012)*
Role of Parents in Treatment

• Critical role in treatment
• Most CBT programs include behavioral training for parents (e.g., attend to and reward their child for engaging in well behaviors and to model well behaviors themselves)
• Need to target parental distress/protectiveness to reduce activity limitations
Teens Taking Charge Program

- Multi-component, multi-media interactive program
  - Disease-related information
  - Self-management skills
  - Social support
- 12 modules for teens (12-18)
- 2 modules for parents
- Health coach (telephone support)
- English and French versions
Pain Squad+ App

System components

Multidimensional pain assessments 2x/day; +/- ad hoc

Self-care advice given based on standardized pain care algorithm (e.g., distraction, social support)

Clinical support from a professional

Re-assessment conducted post-advice (facilitates system learning)

(Lindsay Jibb, PhD Candidate)
PJ’s Treatment

- Pharmacological: Morphine, Tramadol, Lorazepam, Gabapentin in past – not helpful, switched to Pregabalin
- Physiotherapy: Desensitization exercises, but not motivated to do physio exercises
- Psychological: Followed intermittently by oncology psychologist
- CAM: Acupuncture, hypnosis, massage, heat – mildly helpful
- At last visit his body pains had all but gone away (thought to be due to change to maintenance chemotherapy)
Current Pain (/10)

Time and Date of Event

Nurse Contact

Tylenol
Gabapentin
Hydromorphone
Ketamine & Ketorolac
# Psychological and Physical Strategies PJ used

<table>
<thead>
<tr>
<th>Strategy</th>
<th>Effectiveness (/10; M ± SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deep breathing</td>
<td>5.1 ± 2.1</td>
</tr>
<tr>
<td>Mindfulness</td>
<td>5.6 ± 0.8</td>
</tr>
<tr>
<td>Heat</td>
<td>5.8 ± 1.4</td>
</tr>
<tr>
<td>Cold</td>
<td>6.8 ± 0.8</td>
</tr>
<tr>
<td>Massage</td>
<td>5.9 ± 1.8</td>
</tr>
<tr>
<td>Imagery</td>
<td>7.2 ± 0.7</td>
</tr>
<tr>
<td>Distraction</td>
<td>5.0 ± 2.5</td>
</tr>
<tr>
<td>Talking with family/friends</td>
<td>5.6 ± 1.5</td>
</tr>
<tr>
<td>Rest/sleep</td>
<td>5.3 ± 3.8</td>
</tr>
</tbody>
</table>

Overall 212 self-care strategy suggestions were used
Take Home Points

- Awareness of neuropathic pain by patients, their families and health care professionals and access to effective prevention and treatments are the most important factors in preventing or reducing the impact of neuropathic cancer pain in children.

- Be on look out for Neuropathic pain.

- 3 P’s approach is most effective approach.

- Some evidence that concurrent use of gabapentin and opioids provide better analgesia that single doses at higher does.
Future Directions

• Diagnosis – need to develop and valid NeP tools for pediatrics
• Better data on prevalence of NeP in children on and off treatment as well as incidence in long term survivors (e.g., childhood ALL)
• Prospective studies are needed to determine the optimal treatment regimens
Questions?