Learning Objectives

- Review prevalence of pain in children with Neurofibromatosis
- Discuss different kind of pains in children with NF
- Discuss successful interdisciplinary approaches in managing chronic pain and primary pain disorders in children
- Appreciate low importance of pharmacotherapy
Don't have enough staff for pediatric pain control...?

Funny, how there is always enough staff to restrain a child.

Pediatric Analgesia in 1985
“Papoose Boards”

Neurofibromatosis & Pain


- Plexiform neurofibromas (PNs) common and potentially debilitating complications of neurofibromatosis 1: benign nerve-sheath tumors associated with significant pain and morbidity because they compress vital structures.

Neurofibromatosis & Pain

- Plexiform neurofibromas (PNs) and other physical manifestations of NF1 can result in severe acute, neuropathic, and chronic pain.

- PNs may cause nerve compression, airway, and spinal cord compression, leg length discrepancies, and scoliosis. Furthermore, pain is associated with PNs, which tend to grow most rapidly during childhood.

- Pain also may emerge after tumor removal.

- Common nontumor physical manifestations causing pain include skeletal complications and headaches.

- Over 70% of children and adults with NF1 use prescription pain medications.

Pediatric Pain - Status Quo

- Under treatment of pain in children
  - Parents expect pain to be relieved.
  - Priorities of parents of hospitalized children: "Taking care of pain" rated as second highest priority (1st: getting right diagnosis).

- Parents’ greatest distress: failing to protect their child from pain.

- Assumption: everything possible is done.

Pediatric Pain - Status Quo

- USA: adults receive more than two - three times as many analgesic doses as children (with identical diagnoses).

- Compared to adults, pediatric patients receive fewer and/or incorrectly dosed analgesics in daily routine.

- The younger children are, the less likely they receive appropriate analgesia.
Inappropriate Analgesia: Why Bother...

- Children with persistent pain suffer more physical symptoms in adult life, more anxiety and more depression (1946 Medical Research Council and 1958 National Child Development Study).
- Pain ratings at 4-6 months routine vaccination higher for circumcised versus uncircumcised boys. (Taddio A, Katz J, Ilersich AL, Koren G. Effect of neonatal circumcision on pain response during subsequent routine vaccination. Lancet. 1997;349(9052):599-603)

Neurofibromatosis & Pain

- Pain interferes with child’s daily functioning despite 33% taking pain medication.
- Parents: more symptoms of anxiety & larger tumor volumes predicted greater pain interference.
- greater pain interference, worse depressive symptoms, and more disease complications predicted poorer QOL.

Adolescents: more symptoms of anxiety predicted greater pain interference.
- greater pain interference and social stress predicted poorer QOL.
- social-emotional problems mediate the relationship between pain interference and QOL.
- pain interferes with daily functioning in the majority of youth with NFI and PNs even when using pain medication.

So, how do we treat the individual child with NF & pain in front of us?

Hmhh...

Spoiler Alert: Crystal-clear answer on 3rd last slide!
No Needless Pain

That's why we're called

Multimodal Analgesia

https://vimeo.com/20329079

What are we measuring...?

(1) **Nociceptive Pain**: arises from the activation of peripheral nerve endings (nociceptors) that respond to noxious stimulation (e.g., localized, sharp, squeezing, stabbing, or throbbing)
   - **Somatic**: (for example, muscles, joints)
   - **Chronic somatic pain** typically well localized & often results from degenerative processes (such as arthritis)

(2) **Visceral** (internal organs) [poorly localized, dull, crampy, or achy]

(3) **Neuropathic Pain**: resulting from injury to, or dysfunction of, the somatosensory system. [burning, shooting, electric, or tingling]
   - **Central pain**: caused by a lesion or disease of the central somatosensory nervous system

(4) **Psycho-social-spiritual-emotional Pain / Total Pain**

(5) **Persistant (Chronic) Pain**
   - Pain beyond expected time of healing

How Do We Manage Acute Pain in Children?
Nociceptive Pathways & Primary Sites of Action of Analgesics

Injury

Thalamus

Acetaminophen (Paracetamol)

NSAIDs

Basic Analgesics
- Acetaminophen / Paracetamol
- NSAIDs

Multimodal (Opioid-sparing) Analgesia
Citius, Altius, Fortius...?

- Ibuprofen salts: fast-acting formulations
- Advil® Film-Coated Tablets, contains 266 mg of ibuprofen sodium (equivalent to 200 mg of standard ibuprofen)
- Produced significantly better analgesia over 6h, fewer re-medications than standard formulations
- 200-mg fast-acting ibuprofen (NNT 2.1; 95% confidence interval 1.9-2.4) was as effective as 400 mg standard ibuprofen (NNT 2.4; 95% CI 2.2-2.5), with faster onset of analgesia.

- More rapid absorption, faster initial pain reduction, good overall analgesia in more patients at the same dose, and probably longer-lasting analgesia, but with no higher rate of patients reporting adverse events.

- However, earlier onset preferred in other pain condition, such as chronic nociceptive or neuropathic pain.

Ibuprofen-Sodium

- Advil
- Ibuprofen Sodium Tablets

Ibuprofen-Sodium

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Multimodal (Opioid-sparing) Analgesia

- Basic Analgesics
  - Acetaminophen / Paracetamol
  - NSAIDs

- Opioids
  - Tramadol ("weak")
  - Morphine ("strong")

4 WHO-Principles
- "By the clock"
- PRN ("as needed")
- PRN = Patient Receives Nothing
- When pain is constantly present, analgesics should be administered, while monitoring side-effects, at regular intervals
- At analgesic dosing: no sedation expected
Nociceptive Pathways & Primary Sites of Action of Analgesics

Opioids
- Pre-synaptic nerve terminal
  - Neurotransmitter release
- Post-synaptic nerve terminal
  - Membrane hyperpolarization
  => suppress neuronal excitability

Acetaminophen (Paracetamol)

NSAIDs

Regular (!) Pain Assessment

- One-dimensional self-report scores
- Multi-dimensional rating scores

Pain in children with impaired communication

- Non-communicating Children’s Pain Checklist - Revised (NCCPC-R); postoperative Version (NCCPC-PV)

- Pediatric Pain Profile (PPP)

- r-FLACC


Which Opioid to choose?

**Recommended**
- Tramadol
- Morphine
- Fentanyl
- Oxycodone
- Hydromorphone
- Methadone

**NOT Recommended**
- Codeine
- Hydrocodone/Acetaminophen (e.g., Vicodin®)
- Oxymorphone
- Oxycodone/Acetaminophen (e.g., Percocet®)

Multimodal (Opioid-sparing) Analgesia

**Non-Opioids**
- Acetaminophen / Paracetamol
- NSAIDs

**Opioids**
- Tramadol ("weak")
- Morphine ("strong")

4 WHO-Principles
- "By the clock"

**Integrative Therapies**
Such as:
- Massage
- Distraction
- Deep Breathing
- Biofeedback
- Aromatherapy
- Hypnosis

Integrative modalities

- **Integrative modalities effective in management of pediatric pain**
- **yoga**
- **acupuncture**
- **massage**
- **biofeedback**

- **hypnosis**
- **guided imagery**

**Hypnosis**

**Guided Imagery**
- Dobson, C.E.; Byrne, M.W. Original research: Using guided imagery to manage pain in young children with sickle cell disease. The American journal of nursing 2014, 114, 26-36; test 37, 47.

**Hypnosis**
Integrative Pain Management

State of the art pain management in the 21st century demands that pharmacological management must be combined with supportive and integrative, non-pharmacological therapies to manage a child’s pain.


6-year-old Cassandra with severe pain due to chest tube insertion

Fentanyl PCA “the pump” and blowing bubbles “going to bubble land”

Nociceptive Pathways & Primary Sites of Action of Analgesics

- Integration of non-pharmacological therapies
- Periaqueductal grey (endorphins)
- Opioids
- Acetaminophen (Paracetamol)
- NSAIDs
- Injury

Injury

Thalamus

Periaqueductal grey (endorphins)

Integrative (non-pharmacological) therapies

Nociceptive Pathways & Primary Sites of Action of Analgesics

Inhibitory transmitters involved in these pathways incl. norepinephrine, 5-hydroxytryptamine, dopamine & endogenous opioids.

Descending pathways that modulate transmission of nociceptive signals originate in periaqueductal grey and brainstem nuclei to brainstem nuclei to spinal cord.
How does this stuff work...


- Distraction significantly increased activation of cingulo-frontal cortex including orbitofrontal & perigenual anterior cingulate cortex (ACC), as well as periaqueductal gray (PAG) & the posterior thalamus.

- Active distraction techniques, such as imagery, appear to modulate endorphine release in the midbrain, including the periaqueductal grey and thereby increase activity of descending inhibiting pathways thereby decreasing nociception from the dorsal horn resulting in gate pain modulation during distraction.

Nociceptive Pathways & Primary Sites of Action of Analgesics

Multimodal (Opioid-sparing) Analgesia

Non-Opioids
- Acetaminophen / Paracetamol
- NSAIDs

Opioids
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4 WHO-Principles
- "By the clock"

Integrative Therapies
Such as:
- Massage
- Distraction
- Deep Breathing
- Biofeedback
- Aromatherapy
- Hypnosis

Rehabilitation
- Exercise
- Physical Therapy
- Sleep Hygiene
- Occupational Therapy
- Speech Therapy

Psychology
- CBT
Graded Motor Imagery

- Process of thinking about moving without actually moving.

- degree of cortical reorganization correlated with pain intensity

Multimodal (Opioid-sparing) Analgesia

Non-Opioids
- Acetaminophen / Paracetamol
- NSAIDs

Opoids
- Tramadol ("weak")
- Morphine ("strong")

4 WHO-Principles
- "By the clock"

Regional Anesthesia
- Neuraxial infusion
- Peripheral/Plexus Nerve block
- Neurolytic block
- Intrathecal port/pump
- Intraventricular opioids?
- Percutaneous cervical cordotomy?

Integrative Therapies
- Such as:
  - Massage
  - Distraction
  - Deep Breathing
  - Biofeedback
  - Aromatherapy
  - Hypnosis

Rehabilitation
- Exercise
- Physical Therapy
- Sleep Hygiene
- Occupational Therapy
- Speech Therapy

Psychology
- CBT

Regional anesthesia approaches to pain management in PC

- Regional anesthesia:
  - central neuraxial infusions
  - peripheral nerve and plexus blocks or infusions
  - neurolytic blocks
  - implanted intrathecal ports & pumps for baclofen, opioids, local anesthetics, and other adjuvants

- Neurolytic Sympathectomy
  - RCT (n=109) inoperable abdominal or pelvic cancer:
    - better pain control, less opioid consumption, and better quality of life
Neuropathic Pain

Pain arising as a direct consequence of a lesion or disease affecting the somatosensory system (IASP 2008)

- Grading System: (1) Definite, (2) Probable; (3) Possible
- (…but, not all lesions in the somatosensory system lead to neuropathic pain)

Management of Neuropathic Pain in Pediatrics

Suggested “Non-Evidence-based” Step-by-Step Approach

1. Identify and treat underlying disease process (radiation?) (corticosteroids?)
3. Regional anesthesia, if appropriate
4. NEW (!) onset: Opioid analgesics [consider Tramadol or Methadone] plus NSAID
5. Tricyclic Antidepressant (or gabapentinoid) ± low-dose ketamine
6. Tricyclic Antidepressant and gabapentinoid
7. Lidocain patch (if localized pain).
9. Acetaminophen / Paracetamol
10. NSAIDs
11. Multimodal (Opioid-sparing) Analgesia
12. Opioids
   - Tramadol (“weak”)• Morphine (“strong”)
13. 4 WHO-Principles
   - “By the clock”
14. Regional Anesthesia
   - Neuromax infusion
   - Peripheral/Plexus Nerve block
   - Neurolytic block
   - Intrathecal port/pump
   - Electroacupuncture
   - Intravenous analgesia
15. Adjuvants
   - NMDA-antagonists
   - Na-channel blockers
   - Antispasmodics
   - Benzodiazepines
   - Tricyclic antidepressants
   - Muscle relaxants
   - Radioisotopes
   - Bisphosphonate
16. Rehabilitation
   - Exercise
   - Physical Therapy
   - Sleep Hygiene
   - Occupational Therapy
   - Child Life
17. Integrative Therapies
   - Massage
   - Distraction
   - Deep Breathing
   - Biofeedback
   - Aromatherapy
   - Hypnosis
18. Psychology
   - CBT
Neurofibromas & Pain Trials


n=24 children

Chronic Pain in Children

- Pain lasting > 3-6 months: Time definition arbitrary
- Pain that extends beyond the expected period of healing
- hence lacks the acute warning function of physiological nociception

Catastrophizing [“Awfulizing”]

- A set of negative emotional / cognitive processes such as magnification, rumination and pessimism about pain sensations and feelings of helplessness when in pain.
  - **Rumination**: Parent anxious preoccupation with pain
  - **Magnification**: Parent amplification of the significance of pain
- Significant link between child and parent catastrophizing
Fear of Pain

- Plays a significant role in relation to functional disability and depressive symptoms in the context of pediatric chronic pain


- Adolescents with chronic pain less likely to believe benign interpretations of ambiguous bodily-threat information than controls; associated with more disability

- Appears to play both a facilitative and inhibitory role in relation to treatment response:
  - may hinder improvements in disability & depressive symptoms
  - declines are strongly associated with positive functional outcomes

Chronic Pain Pathophysiology


Neurofibromatosis & Pain


- Learning problems and cognitive deficits

- Display social-emotional difficulties, including higher rates of internalizing and externalizing disorders

- Fewer friends

- More social problems compared to normative samples or their unaffected siblings
Psychology
- Anxiety
- Depression
- Stress Sensitivity

Biology
- Genetics (40-50%)
- Microtrauma
- Infection
- Injury

Social
- Early life stressors = acquired vulnerability (50-60%)
- School
- Adverse Events
- Parents: Catastrophizing

Psychology
- Anxiety
- Depression
- Stress Sensitivity

Chronic Pain Pathophysiology

Disordered Pain Processing: Imprecise encoding of threat? Fear of Pain: Catastrophizing

Functional Primary Pain Disorder

Primary Pain Disorders

- Primary headaches
- Centrally mediated abdominal pain syndrome (2016)
- Widespread musculoskeletal pain ("fibromyalgia")
  - CRPS?
- Majority of children experience pain at multiple sites
The Exit Interview

- Pain is real!
- Positive Expectation = Self-fulfilling prophecy?
- Close collaboration with specialist of underlying acute condition to ensure no injury will be caused by rehab treatment
  - Pediatrics
  - Genetics
  - Hematology/Oncology
  - etc.
Exit Interview:
What is the Hard Work...and non-negotiable...?

↑ ↑ Pain

↑ ↑ Stress  Grumpy

↑ ↑ Anxiety
Exit Interview

What is the Hard Work...and non-negotiable...?

- **Physical Therapy**
  - Daily home exercise
- **Integrative Medicine**
  - Self-Hypnosis
  - Biofeedback
  - Progressive Muscle relaxation
  - Daily home exercise
    - Passive: Massage, Acupuncture
- **Psychology** (...if missing school)
- **Normalize Life**
  - Sports/Exercise
  - Sleep-hygiene
  - Social: Having daily fun
  - School: Attending full-time (or school-re-entry plan)
- **Family Coaching**
- **Medications**...??

Opioids & Chronic Pain

- **Lack of evidence** supporting long-term effectiveness
- Escalating **misuse** of prescription opioids including abuse and diversion
- Uncertainty about incidence of **adverse drug events**
  - endocrine dysfunction (androgen deficiency)
- Immunosuppression & infectious disease
- Opioid-induced hyperalgesia
- Xerostomia
- Overdose
- Falls & fractures
- Psychosocial complications
Opioids & Chronic Pain

- Even after adjusting for substantial number of potential confounders, opioids were associated with worse functioning in back pain patients at 6-month follow-up. Ashworth, J., et al., Opioid use among low back pain patients in primary care: Is opioid prescription associated with disability at 6-month follow-up? Pain, 2013. 154(7): p. 1038-44.

1. Low-dose Amitriptyline (stimulates)
2. Gabapentin (inhibits)
3. Acetaminophen
4. Ibuprofen (Celecoxib?)
5. Lidocain 5% patch
6. Melatonin
7. Vitamin D?
8. SSR?
9. Co-Q10, Fish-Oil/Omega 3000, Peppermint oil (coated) [for abdo pain]?

Opioids in the absence of tissue injury or inflammation not indicated!

Exit Interview

Multimodal Analgesia

- Multimodal (opioid-sparing) analgesia: Multiple agents, interventions, rehabilitation, psychological and integrative therapies act synergistically for more effective pediatric pain control with fewer side effects than single analgesic or modality.

Multimodal = Awesome!

2016 Guidelines on the Management of Postoperative Pain


- (Adults): Multimodal analgesia therapy (versus PCA only) reduces length of hospitalization in patients undergoing surgery. (Adapted with permission from the American Society of Regional Anesthesia and Pain Medicine.)
4 steps to make needles less painful

1. Numb the skin
2. Sugar water or breastfeeding for babies
3. Comfort positioning
4. Distraction

Watch videos at childrensMN.org/comfortpromise.

S Friedrichsdorf
@NoNeedlessPain

Ow! I didn’t feel it @childrensmn
ComfortPromise: numb the skin, sitting upright & distract
childrensMN.org/comfortpromise

Do you remember Marius...?

How about a Plan B?
LET Anesthesia

- Sitting upright
- Distraction
- Topical Anesthesia
  - 3mL LET-gel: Lidocaine 4% - Epinephrine 0.18% - Tetracaine 0.5%


If adequate procedural analgesia not feasible with the “4 Non-Negotiables” alone, refer patient to:

(1) Child Life (should’t have been involved by now!)

(2) Needle Phobia: psychology (CBT)

(2) **Mild sedation: Nitrous gas**


or

(3) **Moderate/deep sedation (e.g. ketamine, propofol)**

Note: A sedative alone (such as a benzodiazepine) can **never** be a substitute for procedural analgesia.

What’s Plan B?

So, how do we treat the individual pain patient in front of us?

Crystal clear answer:

“**It Depends**”

-Socrates
Further Links

- The New York Times (June 28, 2016) “Why Aren’t We Managing Children’s Pain?” Covering Dr. Stefan Friedrichsdorf
  [Link](http://well.blogs.nytimes.com/2016/06/27/when-its-not-just-a-boo-boo-the-push-to-treat-childrens-pain/?smid=tw-share&_r=0)


- Video Kiran Stordalen and Horst Rechelbacher Pediatric Pain, Palliative and Integrative Medicine Clinic Tour [Link](https://vimeo.com/122654881)


- Short Movie Meet the Interdisciplinary Chronic Pain Clinic Team at Children’s Minnesota, LittleStars TV [Link](http://www.youtube.com/watch?v=1BkE8dYvQWY)

- Video Tour of the Kiran Stordalen and Horst Rechelbacher Pediatric Pain, Palliative and Integrative Medicine Clinic at Children’s Hospitals and Clinics of Minnesota and an overview of the three programs that are offered at Children’s under this clinic. [Link](https://vimeo.com/123357296)

- Short Movie LittleStarsFilm ’Kali’s Story - Beyond the NICU’ : This amazing pediatric palliative care short movie (7 min) features 8-year-old Kali’s journey at Children’s Hospitals and Clinics of Minnesota from NICU to today, receiving care by the Pain & Palliative & Integrative Medicine program while inpatient, in the clinic, and at home (Jun 22, 2015) [Link](http://www.littlestars.tv/short-films/beyond-the-nicu)

Twitter: @NoNeedlessPain

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Further Training
Contact CIPPC@ChildrensMN.org

11th Annual Pediatric Pain Master Class
- Minneapolis, Minnesota, USA | June 9-15, 2018 [Link](http://tinyurl.com/PedsPMC)

Education in Palliative & End-of-life Care (EPEC)
- Become an EPEC-Peds Trainer Conference, Minneapolis, MN April 12-13, 2018 [Link](http://www.cvent.com/d/qtq1k2)
- Professional Development Workshop, Minneapolis, MN April 14, 2018 [Link](http://www.cvent.com/d/xtq19y)

12th International Symposium on Pediatric Pain (ISPP)
- Basel, Switzerland June 16-20, 2019 [Link](http://www.ispp2019.org)