Chronic, Complex & Common?
Treatment and Prevention of Pain in Children with Noonan-Syndrome

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Learning Objectives

• Define chronic versus acute pain in children
• Review prevalence of chronic pain in children
• Discuss successful interdisciplinary approaches in managing dysfunctional (=primary) pain disorders in children
• Appreciate low importance of pharmacotherapy

5-year old Marius:
Procedural Pain Management

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”

4 Sizes to Fit All Ages

Noonan Syndrome & Pain

- Particular problems related to pain, decreased muscle strength, fatigue, and clumsiness, which had an evident impact on functioning in daily life

- Pain is a frequent and under-recognized clinical feature of NS (n=45; mean 17 years; 2-48 years)

- 62% experienced chronic pain
- commonly in extremities/joints followed by head/trunk
- hypermobile joints = more likely to have pain
- aggravated by colder climate
Noonan Syndrome & Pain


- GERD (60%)
- Constipation (51%)
- Scoliosis (54%)
- Chronic joint pain (54%)
- Depression (49%)
- Anxiety (49%)


- high instance of serious cervical spine disorders, including cervical stenosis, Arnold-Chiari malformation, and syringomyelia
- 81% chronic pain
- 42% pes planus
- 19% pes cavus
- 19% hip contractures
- 12% hand dysfunction (n=3)
- 8% hip dysplasia

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

- 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. (Medical Research Council and National Child Development Study, 1946-1958)


- 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)


- Children (n=48) with injury that led to hospital treatment: Morphine was associated with lower levels of PTSD at follow-up 6 months later. (Nixon RD, Nehmy TJ, Ellis AA, Ball SA, Menne A, McKinnon AC. Predictors of posttraumatic stress in children following injury: The influence of appraisals, heart rate, and morphine use. Bephares Res Ther. 2010 Aug;48(8) 810-5)


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

Hmhh... Spoiler Alert: Crystal-clear answer on 3rd last slide!
How Do We Manage Acute Pain in Children?

- Dosing at regular intervals (“By the Clock”)
- Adapting treatment to the individual child (“With the Child”)
- Using the appropriate route of administration (“By the appropriate route”)
- Using a two-step strategy (“By the Analgesic Ladder”)

WHO guidelines on the pharmacological treatment of persisting pain in children with medical illnesses (2012)
WHO Principle 1: Dosing at Regular Intervals

- **PRN (“as needed”)**
- **PRN = Patient Receives Nothing**
- When pain is constantly present, analgesics should be administered, while monitoring side-effects, at regular intervals
- “By the clock” and NOT as an “as needed” (or pro re nata “PRN”) basis
- Regular scheduling ensures a steady blood level, reducing the peaks and troughs of PRN (“as needed”) dosing
- PRN (as needed) only:
  - May take several hours & higher opioid doses to relieve pain
  - Results in cycle of undermedication and pain, alternating with periods of overmedication and drug toxicity

American Pain Society Principles of Management 2008. 24-27

WHO Principle 2: Adapting Treatment to the Individual Child

- Treatment should be tailored to the individual child and opioid analgesics should be titrated on an individual basis
- At analgesic dosing: no sedation expected
- The effective dose is what relieves the pain
  - Different children may respond differently to same dose
  - Effective dose must be adjusted to child’s needs
  - Dose of strong opioids: only the sky is the limit
- Assess response frequently
  - Pain Scales
  - Look for opioid-induced side effects and toxicity

Assess response frequently
- Pain Scales
- Look for opioid-induced side effects and toxicity

Regular (!) Pain Assessment

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

American Pain Society Principles of Management 2008. 24-27
What are we measuring...

1. Nociceptive Pain: arises from the activation of peripheral nerve endings (nociceptors) that respond to noxious stimulation
   - Somatic (for example, muscles, joints)
   - Chronic somatic pain typically well localized & often results from degenerative processes (such as arthritis)
   - Visceral (internal organs)

2. Neuropathic Pain: resulting from injury to, or dysfunction of, the somatosensory system.
   - Central pain: caused by a lesion or disease of the central somatosensory nervous system

3. Psychosocial-emotional Pain / Total Pain

4. Chronic Pain
   - Pain beyond expected time of healing

Pain in children with impaired communication

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

- Pediatric Pain Profile (PPP)


WHO Principle 4: Using a Two-Step Strategy

**WHO Step 1**
Mild Pain

- Ibuprofen
- and/or
- Acetaminophen (Paracetamol)
- Other NSAIDs? Cox-2 Inhibitor?

**WHO Step 2**
Moderate to Severe Pain

- Morphine
  - or
  - fentanyl, hydromorphone, oxycodone, methadone (UK: diamorphine)


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.

• Physical methods (e.g. cuddle/hug, massage, comfort positioning, heat, cold, TENS)
• Cognitive behavioral techniques (e.g. guided imagery, hypnosis, abdominal breathing, distraction, biofeedback)
• Acupuncture, acupressure, aromatherapy

Integrative Pain & Symptom Management

A Pediatrician’s Top 10 Apps for Distraction & Pain Management http://NoNeedlessPain.org

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


• Chronic Pain in children is the result of a dynamic integration of biological processes, psychological factors, and sociocultural factors considered within a developmental trajectory. Pediatric Chronic Pain Task Force, 2012 American Pain Society
Impact on Family

- Family Life
- Financial Burden (direct medical & indirect)
- Emotional


- Families of children with chronic pain generally have poorer family functioning
- Pain-related disability is more consistent related to family functioning than pain intensity

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

- Kids have higher pain ratings, if either child or mother displays high pain catastrophizing


Fear of Pain

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

- 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
Many different chronic and recurrent pain syndromes, in both adult and pediatric populations, are now considered manifestations of an underlying vulnerability rather than separate disorders. Considerable evidence, especially from twin studies, points to a role of shared biological sensitivity: "pain vulnerability", "pain sensitivity", or "central sensitivity syndrome".
**Functional Primary Pain Disorder**

- Chronic pain disorder that after appropriate medical assessment cannot be explained in terms of conventionally defined medical disease based on biochemical or structural abnormalities
- Associated with significant disruption of everyday life and often incapacitation
- Not typically responsive to conventional medical therapy but responsible for the consumption of enormous medical resources
- Often pejorative implication, i.e. pain is not organic and therefore not real or serious


**Primary Pain Disorders**

- Chronic daily headache
- Centrally mediated abdominal pain syndrome
- Chronic musculoskeletal pain (“fibromyalgia”)
- Majority of children experience pain at multiple sites

*The Porcupine*  
“I Guess That Explains The Abdominal Pains”  
Gary Larson, The Far Side
### Primary Pain Disorder

- **Pain Problem**
- **Medical Workup**
  - **Positive**
  - **Negative**
  - Assume manifestations of underlying vulnerability
- **Chronic-on-acute**
- **Referral to:**
  - Integrative Medicine
  - Mental Health Therapist
  - Pain Clinic

### Chronic-on-acute Pain

- Approximately 5% of children and teenagers in general population have significant pain related dysfunction

- In USA: > 3.7 million children
  - USA - Age 0-17: 74.3 million children

- At least (1%) 5% of children with sickle cell disease, inflammatory bowel disease, rheumatoid arthritis, congenital heart disease, cancer or Noonan syndrome are expected to display chronic pain in addition to their underlying somatic pain episodes

### Interdisciplinary Pain Clinic

- How long can we wait?
- Unknown at what point clinical deterioration begins
- Wait-times for chronic pain treatment of 6 months or longer are medically unacceptable: significant decrease in health related quality of life and psychological well being
  - (metanalysis, 24 studies)
  - Lynch ME, Campbell F, Clark A, Darby PJ, Goldstein D, Peng E
  - In a systematic review of the effects of waiting for treatment for chronic pain Pain 2006 May;131(3): 531-534
- 2/3 of US pediatricians felt it was not their primary responsibility to treat chronic pain
Who do we need?
Psychology & Physical Therapy!

- **Physical activity** reduces risk for depression in female adolescents

- **Adolescents with chronic pain:** lower physical activity level

- **Psychological Treatments** significantly reduce pain intensity reported by children and adolescents with headache, abdominal pain, and fibromyalgia.

- **Cognitive-behavioral therapy** increases prefrontal cortex gray matter in patients with chronic pain - associated with reduced pain catastrophizing.

- **Meta-Analysis:** Yoga may be useful for several pain-associated disorders

- **n=5 adolescents with rheumatoid arthritis:** 6-week, bi-weekly Iyengar Yoga: improvements in pain, pain disability, depression, mental health, vitality, self-efficacy
  Iyengar Yoga for Young Adults with Rheumatoid Arthritis Results from a Mixed Methods Pilot Study / Pain Symposium, 2010 May. 39(6):10-13.
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
  - Rheumatology
  - Gastroenterology
  - Hematology/Oncology
  - etc.
Exit Interview:
What is the Hard Work...and non-negotiable...?

Sleep & Chronic Pain

- Majority of children with chronic pain have sleep difficulties; problems with:
  - Sleep initiation
  - Maintaining sleep
  - Early morning awakening

- Insomnia: 12-18 years with chronic pain: 54% (vs 20% control)

- Sleep problems are persistent (50% vs 20%) and associated with negative impact for youths with chronic pain

- Treatment of insomnia in youths with chronic pain may lead to improvements in QoL and reduction in healthcare cost.

School & Chronic Pain

- Long-term school impairment -> poorer academic and occupational achievement, increase educational costs, development of psychiatric disorders

- Parental pain catastrophizing and parental protective response to child pain each individually predict school attendance rates and reports of overall school impairment.
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...???**

Medications?

![Ritalin Ad](https://via.placeholder.com/150)
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

Updated Cochrane Review: Effectiveness/safety of long-term opioid therapy for lower back pain remains unproven


- Even after adjusting for substantial number of potential confounders, opioids were associated with worse functioning in back pain patients at 6-month follow-up


109 patients with chronic pain over 7 years: NO relation between opioid dose change and clinical pain score


Exit Interview

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

Opioids in the absence of tissue injury or inflammation not indicated!
Chronic Pain & Vitamin D

- Low vitamin D appears to be a marker of chronic disease, not causing pain / chronic disease (exception: osteopenia) - Autier P et al. Vitamin D status and health: a systematic review. The Lancet Diabetes & Endocrinology Volume 2, Issue 1, Pages 76 - 89, January 2014


Melatonin = analgesic?


- Concerns about melatonin and sexual development issues in adolescents ??

Do you remember Marius...?

How about a Plan B?
LET Anesthesia

- Sitting upright
- Distraction
- Topical Anesthesia

- 3mL LETgel: Lidocaine 4% - Epinephrine 0.18% - Tetracaine 0.5%


Further Reading

Conquering Your Child’s Chronic Pain
A Pediatrician’s Guide for Reclaiming a Normal Childhood
Lonnie K. Zeltzer, M.D.
Hanna, Pelham, New York, 2001-2012
and Christina Blackett Schrank

Help Your Child or Adolescent
Regain Power over Pain, Restore Function, and Well-Being

HarperResource
$ 14.95

PainBytes

The mystery of chronic pain https://www.youtube.com/watch?v=6--CMhcCfQ

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

Crystal clear answer:

“It Depends”
-Socrates
Conclusion

- Chronic Pain in Children, teenagers with Noonan syndrome is common, under-assessed, and under-treated
- Many clinicians have historically considered most chronic pain to be largely from peripheral nociceptive input (i.e. damage or inflammation), and data increasingly suggest this is simply not the case

- Many different chronic and recurrent pain syndromes are now considered manifestations of an underlying vulnerability rather than separate disorders
- Opioids in the absence of tissue injury or inflammation are contraindicated!
- Importance of rehabilitative, interdisciplinary team approach.

With profound gratitude to our interdisciplinary Pain, Palliative & Integrative Medicine team

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Music Therapy
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Admin Assistants
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- Cheryl Pearson

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- Brock Habert
- Alisa McGlade

Manager
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Further Links

- Video: Kiran Stordalen and Horst Rechelbacher Pediatric Pain, Palliative and Integrative Medicine Clinic Tour [Link](https://vimeo.com/122654881)
- “Children’s Comfort Promise: Doing everything possible to treat and prevent pain.” Eliminating Needle Pain in children [Link](http://vimeo.com/106286508)
- Short Movie: Meet the Interdisciplinary Chronic Pain Clinic Team at Children’s Minnesota LittleStars TV [Link](https://www.youtube.com/watch?v=XkhEc11Hb4A)
- 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/123357294)
- Short Movie: LittleStarsFilm  'Kali’s Story - Beyond the NICU’ This amazing pediatric palliative care short movie (7 min) follows 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)

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Further Training

10th Annual Pediatric Pain Master Class
· Minneapolis, Minnesota, USA | June 17-23, 2017
Education in Palliative & End-of-Life Care (EPEC), Become an EPEC-Pediatrics Trainer
- Montréal, Québec, Canada | April 29-30, 2017 (Professional Development Workshop: 04/28/17)
Contact: CIPPC@ChildrensMN.org