Chronic Nociceptive and Neuropathic Pain in Infants and Children and in Developing Animals

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1. Overview

Chronic nociceptive pain and chronic neuropathic pain are sources of enormous distress and economic loss in adults. Disorders such as low back pain, recurrent headaches, degenerative arthritis, and diabetic neuropathy are all extremely common in adults.

The aim of this lecture is to address the following questions:
1. How does the epidemiology and clinical course of chronic nociceptive pain and chronic neuropathic pain differ among adults and children?
2. What can animal models and human physiological studies tell us about the mechanisms underlying age-related differences in the incidence, prevalence, severity, and clinical course of chronic pain in infants and children?
3. What is the evidence for or against the safety and efficacy of various treatments for neuropathic pain in children? When is extrapolation from adults likely to be valid or harmful? How might we approach clinical trials for neuropathic pain in infants and children?

2. Chronic Pain in the Elderly

“Old age ain’t no place for sissies.”
- commonly attributed to Bette Davis, also ascribed to H.L. Mencken

Many types of chronic pain are much more prevalent with advancing age. Chronic nociceptive pain associated with skeletal degeneration is nearly universal among 70-90 year olds. Surveys of the elderly document a very high prevalence of chronic pain in the spine, hips and knees. Two forms of neuropathic pain, post-herpetic neuralgia and trigeminal neuralgia, are predominantly disorders among the elderly; > 70 % of all cases of both of these disorders have onset of symptoms after age 60, and both are relatively rare before age 35.

Some mixed pain disorders, e.g. radiculopathy due to disc herniation, TMJ disorders, and carpal tunnel syndrome, are commonly cited as being more common in younger adults

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and middle-aged adults than among the elderly, though this may reflect referral patterns among specialist physicians rather than true population-based epidemiology. It is plausible that, if there is a higher prevalence of these disorders in middle age, that workplace-related physical demands and emotional stressors may play roles in the higher frequency in this age group.

3. Recurrent or Intermittent Pain Conditions in Childhood Versus Chronic Persistent Pain Conditions

The common pain problems seen in everyday pediatric practice are recurrent, rather than chronic and persistent. That is to say, a high percentage of children (5-10% of school aged children and early adolescents) in school-based studies will experience recurrent episodes of pain on some days (especially headaches, abdominal pains, chest pains, and limb pains) alternating with many days of no pain [1] [2] [3] [4]. In general, these disorders are not associated with major organ pathology, and these children are overall medically quite well. Even with these common disorders, much of treatment is based on custom, rather than clinical trials[5]. Evidence supports the robust utility of a range of cognitive-behavioral interventions for reducing pain and improving functioning for children with a number of recurrent pain disorders[6] [7] [8]. Conversely, chronic persistent pain, i.e. pain occurring nearly every day, is relatively less common in pediatrics, though these children are being referred in increasing numbers to pediatric pain specialists.

4. Chronic Nociceptive Pain in Infants and Children

Inflammatory arthritis
1. common in adults, less common in children
2. over the past 30 years, treatment of JRA has changed radically, with a much greater emphasis on early use of disease-modifying, immuno-modulatory treatments
3. in developed countries, severe chronic pain is now a relatively uncommon finding with JRA in children, though a subgroup of patients still present to pediatric pain clinics; subgroups include: (a) those with more severe involvement of their arthritis or delayed diagnosis with joint destruction, (b) those with related disorders such as scleroderma or mixed connective tissue disease, or (c) those with greater difficulty with coping with pain[9].

Degenerative musculoskeletal disorders
1. nearly universal among the elderly, relatively uncommon in children
2. common conditions generating referrals to a pediatric pain service: hemophilia, sickle cell disease, unfixable congenital hip dysplasia, hip degeneration with neuromuscular disorders, unfixable or degenerative spine disorders, osteogenesis imperfecta, connective tissue disorders (e.g. Ehlers Danlos)
3. surgical interventions sometimes improve pain, but data are scarce unsolved problem: which children with hip pain associated with cerebral palsy, spasticity, and hip degeneration should have a pelvic osteotomy, a hip fusion, a femoral head resection, botox, phenol obturator blocks, oral antispasm

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medications[10], an intrathecal baclofen pump [11], selective dorsal rhizotomies….etc.

Chronic Visceral Pain
1. irritable bowel syndrome, endometriosis, and interstitial cystitis are all relatively common in adults; all are seen with some frequency in adolescents [12], less common in younger children. Pelvic pain due to endometriosis can occur even before first menses; referrals to our clinic are not rare in 11-13 year old girls.
2. Chronic pelvic pain is not uncommon among children following gastric augmentation to the bladder: hormone-induced acid secretion into the neo-bladder may be suppressed by proton-pump blockade.
3. Studies of adults with irritable bowel syndrome indicate a substantial percentage had an onset of symptoms as episodic abdominal pain in childhood [13].
4. Visceral neuropathic pain is a relatively common problem in children with some severe neurodegenerative disorders, including mitochondrial disorders. Neuropathic pain medications are often tried; there is little evidence. Occasional patients receive either short courses of thoracic epidural analgesia or celiac plexus blockade. Again, outcomes are entirely anecdotal.
5. Unknown: Is colic among infants a form of visceral pain and hyperalgesia?

5. Neuropathic Pain in Infants and Children [14]

Diabetic Neuropathy
1. Very common source of distress and suffering in adults
2. Rarely symptomatic in children unless duration of diabetes > 10 years
3. Despite lack of pain reports, children with diabetes commonly have measurable abnormalities on NCV/EMG studies and on autonomic testing [15].
4. Better diabetic control appears to be associated with improved measures of nerve conduction.
5. Treatments extrapolated from adults: tricyclics [16-18], anticonvulsants [19], SNRIs.

Post-Herpetic Neuralgia
1. Common source of distress and suffering in adults
2. Risk in adults increases dramatically with age.
3. Vaccination in adults age > 60 reduces risk of cutaneous zoster and PHN.
4. In developed countries, cutaneous zoster is moderately rare in children, but seen with some frequency – Iceland – incidence 1.6/1000/year [20].
5. Occurrence in otherwise healthy children in developed countries does not imply a high risk of malignancy or immunodeficiency.
6. Icelandic study: if children with zoster are otherwise healthy, essentially none had pain after 1 month [20].
7. Unknown: how will widespread zoster vaccination in childhood affect the long-term natural history of cutaneous zoster and PHN in both children and adults?
8. PHN in pediatric tertiary centers is most commonly with malignancy, immunodeficiency.

9. If the child has immunodeficiency or other risk factors, recommend early use of antiviral agents, e.g. famcyclovir; if the child is healthy, antiviral drugs are not the standard of care for uncomplicated cutaneous zoster.

10. In sub-Saharan Africa, zoster is commonly associated with HIV infection.

11. treatments extrapolated from adults [21]: tricyclics [22], anticonvulsants[23], opioids, SNRIs, epidural local anesthetics and steroids, intrathecal steroids

Pain After Amputation
2. Risk in adults increases dramatically with pre-amputation pain.
3. Frequency in adults depends on inclusion criteria, ranges from 30-80%.
5. Amputation causes cortical reorganization[26] – the sensory homunculus you studied in medical school is not immutable, and greater degrees of reorganization of the homunculus are correlated with greater intensity of phantom pain.
6. Treatments that relieve phantom pain tend to revert the homunculus to a pre-amputation pattern. Patients whose phantom pain responds to opioids show more reversion of the homunculus than those who do not[27].
7. Treatments that emphasize purposeful use of a myo-electric prosthesis or a mirror-image limb presentation in physical therapy appear effective in reducing phantom pain and “normalizing the homunculus” [28].
8. Contrary to prior belief, phantom pain is relatively common in children following amputation [29] [30].
9. Gabapentin has been used with a suggestion of benefit in one retrospective pediatric case series [31].

Pain After Brachial Plexus Injury
1. In adults, this is a common problem among motorcyclists and in wartime
2. In adults with brachial plexus injury, risk of prolonged moderate or severe pain > 70%
3. In pediatrics, > 90% of plexus injuries occur in newborns with traumatic delivery, e.g. shoulder dystocia or aggressive use of forceps[32].
4. Unlike adults, pain appears exceedingly rare following newborn plexus injury
5. McCann et al [33]: pain or self-mutilation almost never seen in cases without surgery or in those having orthopedic operations; pain or self-mutilation for several months to up to 2 years in 1/3 of infants having nerve dissection or nerve grafting procedures.

Reflex Sympathetic Dystrophy (RSD)/ Complex Regional Pain Syndromes (CRPS)
1. In adults, estimates of prevalence and severity vary widely. Diagnostic criteria have varied in previous studies. A consensus group affiliated with IASP has developed and tested diagnostic criteria [34] [35].

2. Literature from adult pain clinics would suggest that this is generally a severe disorder with a poor prognosis.

3. Population-based epidemiology (e.g. Mayo Clinic studies of Olmstead County, MN) suggest that there is a spectrum of milder forms of the disorder, and that there is a much more favorable prognosis overall.

4. Evidence for medical and invasive treatments in adults is poor - there is only limited evidence for efficacy of most medications, including free radical scavengers[36], most types of nerve blocks, or sympathectomy [37] [38]. Evidence is better for rehabilitative treatments that emphasize a return to normal use of the affected limb[39] [40-42]. In our clinic, regional anesthetic infusions are used on occasion to initiate limb movement and facilitate physical therapy [43, 44].

5. Even for spinal cord stimulation, which had a positive clinical trial in NEJM by Kemler et al[45], the authors recently published a followup letter showing very little long-term benefit at 5-year follow-up in their original cohort[46].

6. Controversy persists regarding the roles of psychological factors in either causation, amplification or perpetuation of pain and disability in CRPS, both in adults [47] [48] [49] and in children [50] [51].

7. In children, RSD/CRPS is very rare before age 6, incidence appears to increase dramatically around age 10. In children and adolescents, there is a marked female: male preponderance, and a marked lower extremity preponderance. Autonomic signs and symptoms may fluctuate over time[52]. Many of the patients show abnormalities on quantitative sensory testing[53] (QST); about 1/3 of subjects in our practice show signs of minor nerve injury, consistent with CRPS2 (Meier, Sethna, Zurakowski, and Berde, manuscript under review).

8. In a randomized controlled pediatric trial, outpatient physical therapy (either once or 3 times weekly) and cognitive behavioral treatment was associated with good improvement in pain and very good improvement in gait and limb function over a 6 week period[54].

9. Long-term prognosis in children and adolescence is very favorable [55] [54] [56] [57]. > 90% have full recovery, although 25% will have a second episode at some point over a 2-5 year period.

**Lumbar disc herniation and radiculopathy**

1. Radiculopathy due to herniation of either lumbar or cervical discs is the most common form of neuropathic pain in young adults and in middle age.

2. Lumbar radiculopathy is rare in children and relatively uncommon in adolescents; cervical radiculopathy appears very rare in children and rare in adolescents.

3. Overall in adolescence, back pain is more commonly associated with muscle and ligament strain, hyperlordotic strain, spondylolisthesis, spondylolysis[58]…

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4. In our clinic (with an in-hospital referral base of 22 attending pediatric orthopedic surgeons and 6 attending pediatric neurosurgeons), about 50 new patients with sciatica and disc herniation are seen annually (roughly 1 per week).

5. The entire pediatric literature on lumbar disc herniation with radiculopathy concerns < 600 cases; several publications in neurosurgical literature say that outcomes of discectomy surgery are very good. There are only scarce data on the natural history and clinical course of lumbar radiculopathy in children who do not undergo surgery. A large-scale, long-term clinical outcome study is in progress.

6. Demographics in adolescents – seems to be three predominant groups
   a. active athletes (football, gymnastics, dance, wrestling…)
   b. morbid obesity
   c. hyperlaxity or connective tissue disorders

7. Treatments are extrapolated from adults. While many of the adult studies are of poor quality, systematic review as discussed by the Oxford Evidence-Based Medicine Bandolier group (http://www.jr2.ox.ac.uk/bandolier/) suggest that epidural steroid injections provide substantially better short-term (up to 2 month) pain relief than placebo interventions. In my opinion, the interpretations given in these meta-analyses may underestimate the clinical benefit with optimal current-day technique, because some of the negative studies on epidural steroids in adults suffer from the following limitations:
   a. Inappropriate patient selection
   b. Injection without fluoroscopic guidance
   c. Use of interlaminar approach instead of the transformaminal approach

8. Our general approach is to perform most epidural steroid injections via transformaminal approach with fluoroscopic guidance, and with concomitant selective nerve root blocks. Pain relief at rest and with straight leg raising while the local anesthetic root block is present is regarded as one positive factor among several in guiding decisions about operative microdiscectomy.

**Spasticity and poorly localized distress in children with neurologic disabilities**

1. “Screaming of unknown origin” - approach to the neurologically devastated child with persistent distress, agitation or screaming.

2. Drug treatment for spasticity is often performed in a very imprecise manner. There is a need for better clinical trials to define risks, benefits, and side-effect profiles of the commonly used medications for spasticity[10].

6. **Selected Animal Models**

**Surgical Incisions in Neonatal Animals**

Brennan and coworkers have developed several pain models involving standardized surgical incisions in rats. These models permit examination of mechanisms underlying pain and hyperalgesia following surgery.
Ririe and coworkers have adapted Brennan’s paw incision model to examine age-dependence of post-surgical thermal and mechanical hyperalgesia\[59\]. The design and interpretation of studies using this type of model is made more challenging by the marked age-dependence of thermal and mechanical withdrawal thresholds in intact (non-operated) animals. Two week old rats showed more rapid recovery to near-baseline mechanical responsiveness than 4 week old and 16 week old rats. Resolution of thermal hyperalgesia showed no such age dependence. Selective COX-1 and selective COX-2 inhibition partially reversed incision-induced mechanical hyperalgesia in 4 week old rats; both were entirely ineffective in this effect in 2 week old rats\[60, 61\]. Remarkably, COX-1 inhibition was more effective in reversing thermal hyperalgesia in 2 week old rats compared to 4 week old rats, while COX-2 inhibition had no effect on thermal hyperalgesia in 2 week old or 4 week old rats\[60, 61\].

Traditionally, surgery and trauma have been examined for effects in activating local (peripheral) and systemic inflammatory responses. NSAIDs and COX-2 inhibitors have been regarded as predominantly peripherally-acting analgesics, unlike opioids and other agents that act predominantly in the central nervous system. However, a growing body of literature implicates activation of spinal inflammatory mechanisms in many forms of pain and hyperalgesia\[62\]. Peripheral injury, limb inflammation, or surgical incisions all produce a series of spinal events, including activation of microglia, increased expression and activation of cytokines and prostanoids in spinal microglia and neurons\[62\].

Ririe and coworkers have shown recently\[63\] (i.e. to be presented next week at the ASA) that paw incision produces microglial activation in 4 week old and 16 week old rats, but not in 2 week old rats.

Can we use these rat studies to derive some implications for a very basic, simple, and unanswered clinical question: should we give NSAIDS, e.g. ibuprofen, as postop analgesics to, for example, 2-month old infants?

Reasons in favor:
1. in older children and adults, NSAIDs are good analgesics
2. they don’t depress respiration,
3. in older children and adults, NSAIDs are opioid-sparing
4. there are pretty good short-term safety studies for ibuprofen when used for closure of ductus arteriosus in sick preterm neonates
5. there is good safety when ibuprofen is used for fever control in very large studies of infants and toddlers
6. PK is known for IV ibuprofen from ductus arteriosus studies

Reasons against:
1. there are essentially no analgesic studies showing efficacy below age 3 months
2. Ririe’s infant rat COX studies raise the question of whether NSAIDs might be less effective in neonates and young infants.
Spared nerve injury model

Many forms of nerve injury seem to generate a different pattern of consequences in infant rats, compared to adult rats[64].

One of the better models of peripheral neuropathic pain in adult rats, developed by Decosterd and Woolf, involves section and ligation of the tibial and common peroneal nerves just below the trifurcation of the sciatic nerve, with sparing of the sural nerve. This “spared-nerve-injury” model produces allodynia and pain behaviors lasting up to 6 months in adult rats.

Work by Howard and colleagues showed that, when this type of injury was performed in rats up through 3-4 weeks of age, the rats did not exhibit allodynia or pain behaviors[65]. The molecular mechanisms underlying these age-related differences are receiving more detailed scrutiny in several laboratories. In the spared nerve injury model, infant rats show a diminished activation of cytokine responses in spinal microglia.

It is intriguing to correlate the age-dependence of neuropathic pain in this rat model with age-related changes in incidence of RSD/CRPS in humans. 5 weeks of age in a rat roughly resembles neurologic development in school-age or early adolescence in humans, which is the common age of onset of RSD/CRPS.

Visceral hyperalgesia

Al-Chaer and coworkers developed a model of visceral hyperalgesia in adult rats by creating an inflammatory injury to the bowel at specific developmental stages in infant rats. They propose this as a model of irritable bowel syndrome in humans, and speculate that early traumatic events (both physical and emotional) may contribute to the pathogenesis of these disorders in humans. Anand and coworkers[66] have argued that gastric suction at birth may predispose to subsequent visceral pain disorders; others have disagreed[67].

Opioid Tolerance: The Downside of Youthful Neuroplasticity

In many respects, youth is a good thing. Running backs, gymnasts, super-models, swimmers, and even mathematicians all tend to be more successful in their chosen careers in their 20s and 30s compared to their 50s and 60s. As noted above, chronic pain is common in 70 year olds, relatively uncommon in children.

Chronic administration of opioids for non-cancer pain remains a controversial area, both for adults[68][69]; very little is known regarding risk-benefit ratios of long-term opioid use for children with chronic non-cancer pain.

In the case of opioid tolerance, however, animal and human data by Palmer and coworkers suggest a specific disadvantage of being young: younger animals[70] and younger humans[71] develop tolerance to opioids more rapidly than older animals and
older humans, respectively. Palmer examined development of opioid tolerance in young adults and older adults at the UCSF pain clinic, and noted much more rapid development of tolerance in the younger adults compared to the older ones [71]. Observations of infants in intensive care and children and adolescents with advanced cancer [72] support the view that rapid dose escalation is much more of a problem in pediatric intensive care and pediatric oncology than in their adult counterparts.

Does this mean that opioids should be avoided in infants and children? Certainly not. However, it may imply that, in settings where opioid use is likely to be prolonged, greater consideration should be given to strategies that will slow the development of tolerance, either by:

1. optimal use of non-opioid analgesics for the purpose of opioid-sparing, including regional analgesia, NSAIDs, anticonvulsants, antidepressants,
2. co-administration of anti-hyperalgesic agents specifically to prevent or reverse tolerance (possibly low-dose ketamine, clonidine, anticonvulsants such as gabapentin, or antidepressants), or
3. early selection of opioids with a lower rate of development of tolerance, e.g. methadone or buprenorphine.

In children with advanced cancer who have logarithmic escalation of opioid dosing, where appropriate, our preference is to use implanted intrathecal ports [73] for infusion of combinations of local anesthetics, opioids, clonidine, and (in unusual cases) ketamine.

Models of opioid tolerance in animals emphasize the importance of several pathways:

1. NMDA receptor-mediated activation of ion channels and several second messenger systems,
2. opioid-receptor-G-protein-coupled changes in intracellular signaling involving cyclases, protein kinases, calmodulin, and inositol-phosphates, and
3. opioid-receptor endocytosis and intracellular recycling of the receptors.

The RAVE (receptor-activation-versus-endocytosis) hypothesis correlates the greater development of opioid tolerance with greater activity at receptor-mediated activation of protein kinases versus activity in inducing endocytosis of opioid receptors. High RAVE index opioids such as morphine and oxycodone generate tolerance more rapidly than low RAVE index opioids such as methadone and buprenorphine.

Effects of Regional Anesthesia on Pain, Hyperalgesia, and Molecular Consequences of Inflammation, Surgery, or Nerve Injury

The clinical literature on effects of different types of regional anesthesia on outcomes after surgery in adults suggests a variety of short-term and longer-term beneficial effects[74]. Effects on regional anesthesia on prevention of neuropathic pain in adults have varied, with differences in patient selection, in approaches used to interrupt afferent activity, and in outcome measures[75]. Animal models of effects of regional anesthesia on responses to injury have also produced variable results [76] [77] [78]. In two recent studies, Beloeil et al [79, 80]
sought to clarify effects of prolonged nerve blockade on local, systemic, and spinal inflammatory responses. Bupivacaine and the site 1 sodium channel toxin tetrodotoxin showed similar effects on peripheral and spinal inflammatory responses, but they have very different actions in suppressing systemic inflammatory responses. Effects of regional blockade on pain responses in rats are age-dependent [81] [82] [83].

**Long-term consequences of inflammatory injury or brief noxious procedures in rats and in humans.**

Several groups have examined long-term consequences of inflammatory injury or brief noxious procedures in infant rats, and modification of these responses by analgesics. These models may be difficult to interpret due to effects unrelated to pain per se. For example, rat pups may be regarded differently by their dams (mothers) following surgical procedures or following a repeated inflammatory stimulus, and changes in maternal-infant interaction may contribute to effects on behaviors and neurologic development unrelated to pain per se. Similarly, interpretation of long-term effects of pain and pain treatment in critically-ill neonates is complex, since painful episodes are more common among neonates with a variety of risk factors for developmental disabilities[84].

7. **Conclusions**

1. Several forms of chronic inflammatory and neuropathic pain show age-related changes in incidence, clinical presentation, natural history, and responses to treatment.
2. Development of infant animal models for post-surgical pain, inflammatory pain, peripheral somatic neuropathic pain, and visceral pain may help elucidate mechanisms underlying the observed age-related differences in the presentation and course of analogous pain disorders in humans.
3. Clinical trials of treatments of chronic pain in children will require innovate designs, recognition of some unique ethical and practical constraints, and development multi-center clinical trial consortia to permit adequate sample sizes and economies of scale.

**References**


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