Needle Pain in Children: Contextual Factors

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Financial Disclosure: Dr Walco received travel expenses and an honorarium from Anesiva, Inc for participation in the roundtable.

ABSTRACT
Pediatric pain experiences result from a complex interplay of genetic, experiential, and developmental factors. These elements, as they relate to needle-stick procedures and other relevant painful phenomena, are explored in this article so that the context of possible interventions may be more fully appreciated. Clinical implications are discussed incorporating ethical perspectives. Pediatrics 2008;122:S125–S129

Pediatric health care providers are committed ethically and morally to “do no harm” to their patients. Exposing a child to pain that is treatable, especially if long-term deleterious effects may be associated with that pain, is inconsistent with the do-no-harm doctrine and, therefore, is unethical.1 How much pain or distress is generated by a particular bodily insult or pathologic condition is determined not by the health care provider but, rather, by the patient.1,2 Although health care professionals and adults often view venipuncture or intravenous (IV) catheter insertions as quick, routine, and relatively painless, data are unambiguous that children consider the pain associated with such procedures to be “clinically significant” and distressing.4

Pediatric pain experiences result from a complex interplay of genetic, experiential, and developmental factors. These elements, as they relate to needle-stick procedures and other relevant painful phenomena, are explored in this article so that the context of possible interventions may be more fully appreciated, thereby potentially improving their impact. We are only now beginning to understand the long-term implications of early pain experiences in children, including venous access pain, and additional investigation is encouraged. What follows is a brief review of current thinking on the development and impact of the pain response in the young. The intention is to provide the reader with a perspective on current research and clinical endeavors pertaining to this issue.

KEY FACTORS THAT SHAPE THE PAIN RESPONSE
As is the case with so many developmental phenomena, children’s reactions to minor invasive procedures are determined by genetic bases that interact with environmental events. Certainly the general course of development of the nervous system is genetically determined; therefore, the basic elements of nociception and pain response are fairly predictable. Within that, however, one’s specific life experiences may lead to individual differences in response that are of clinical importance.

A paradigm that is useful for organizing these effects was introduced by McCall5 in 1981. The “scoop” model of development (see Fig 1) posits a fairly predictable course of development from conception through the early stages of life that is primarily preprogrammed by genetics, a developmental pathway that can be likened to a ball rolling down the center of a scoop or a trough. In most cases, this maturational trajectory is rather robust, but it may be affected by environmental influences. Many of these environmental influences may have relatively transient effects that can be likened to knocking the ball off course temporarily followed by the ball’s eventual return to its normal course. This would be indicative of an individual difference in development, and because the course is righted, clinical concern may not be high. In contrast, other forces may have more a profound impact, which may propel the ball far enough off course that a lasting individual difference is created. These latter effects are typically of substantial clinical interest. Thus, our concern is in understanding those environmental insults that irreversibly alter the course of nervous system development or functioning, which in the context of the current discussion would manifest as a maladaptive pain response.

Research on the inherited elements of the pain response, the “nature” part of the equation, has typically focused on the overall predictable course of pain-response maturation, the impact of unique genetic influences, and the role of temperament in the pain response. The preceding endowments predispose an individual to use related coping strategies in response to various life experiences (ie, the “nurture” part of the equation). Over time, response styles emerge that may be predictive of adjustment to painful situations. Of course, our ultimate concern would be the avoidance of maladaptive pain or coping responses as individuals develop and mature over time.
The Development of Pain Pathways

Understanding of the ontogeny of the pediatric pain experience has increased significantly in the past 2 decades. Accumulating evidence has demonstrated that pain is perceived earlier in life than had been previously believed. For example, a little more than 30 years ago, it was thought that infants did not feel pain, and if they did, there was no lasting memory of the pain. Today, it is clear that very premature neonates experience pain, and the "lower limit" of the age at which pain systems are intact continues to be revised downward. Indeed, recent data on fetal pain lend support to the view that pain systems develop and function very early in the gestational period.

Nociception refers to the excitation of peripheral afferent neurons in response to a noxious stimulus. Axons of these peripheral sensory nerves terminate at synapses in the dorsal horn of the spinal cord. Reflex arcs involving interneurons in the spinal cord produce reflexive responses, such as withdrawal from the stimulus. In addition, neurons ascend through the spinal cord to the brain, where higher centers are stimulated and the painful stimulus is first perceived. Thus, nociception is merely sensory excitation, whereas pain is the subjective perception of this sensory excitation and the usual focus of clinical concern.

Animal models have shown that sensory nerve fibers involved in nociception grow out of the dorsal root ganglia during the prenatal period and eventually innervate the skin in a somatotopically manner. These sensory neurons are generated in 2 waves, with large-diameter tyrosine kinase receptor C– and B–expressing (TrkC+ and TrkB+) neurons arising initially, followed by small-diameter tyrosine kinase receptor A–expressing (TrkA+) neurons. The larger-diameter A fibers migrate first from the dorsal root to the periphery to form a cutaneous nerve plexus, which is followed by migration of C fibers. In addition, centrally directed dorsal root fibers reach the lumbar cord, again with A fibers penetrating the gray matter first, followed by C fibers. From the outset, these fibers terminate in a somatotopically precise manner, with reflex arcs beginning to develop shortly thereafter. The last elements to appear are descending fibers from the brainstem, which modulate excitation and inhibition.

Several short-term and long-term consequences of tissue damage during this developmental period have been reported. After injury, significant C-fiber activation occurs over a prolonged period of time, and these fibers can be sensitized further by inflammatory chemicals. Repetitive stimulation evokes a "wind-up" in which response amplitude increases with each subsequent stimulus. Therefore, injury may result not only in an immediate nociceptive response but also in hyperalgesia and allodynia over later times.

Although many nervous system responses may resolve after an injury has healed (ie, the ball may fall back into the trough), tissue damage during certain critical periods of development may have a more lasting effect, even into adulthood. An array of possible mechanisms exists to account for this, including alterations in synaptic connectivity and signaling, changes in the balance of inhibition versus excitation, and increased terminal density in the injured area resulting from increased concentrations of nerve growth factor. Although this remains an emerging area of study in rodent models, Fitzgerald has demonstrated analogous hyperalgesic effects in human studies as well.

Early postnatal pain may also impact neurodevelopment through stress responses. In a study designed to evaluate the relationship between early pain and stress, rat pups were divided into 3 groups during the first 7 days of life and received (1) paw touches or needle pricks every day, (2) paw touches or needle pricks every other day, or (3) no treatment. Repeated pain experiences seemed to affect subsequent responses to open-field habituation, an index of emotionality, at 4 weeks of life; some gender differences were noted as well. Although human socioemotional development is far more complicated than that of rats, these data suggest that early pain experiences affect neurodevelopmental function in the mature organism.

Genetics of the Pain Response

In a review of the role played by genetics in the pain response, Mogil et al maintained that it is unlikely that a simple genetic basis will be found to account for individual variability in pain response. Only a few genetic mutations or polymorphisms have been identified that account for specific pathologic pain states in humans (eg, congenital insensitivity to pain and familial hemiplegic migraine). Beyond this, most genetic information has been derived from studies that involved animal models (typically mice) and focused, in particular, on differences in nociception and sensitivity to analgesia. The genetics of pain in humans seems to be far more complex than in other species, but additional data will undoubtedly emerge over time, including data from clinical investigations.

In a recent study, children aged 4 to 10 years who were undergoing insertion of an IV catheter received pretreatment with 1 of 2 topical lidocaine anesthetic creams: lidocaine and prilocaine cream, 2.5%/2.5% (EMLA [eutectic mixture of local anesthetics] cream [AstraZeneca LP, Wilmington, DE]), or liposomal lidocaine 4% (LMX4 topical anesthetic cream [Ferndale...
Laboratories, Inc, Ferndale, MI). On the basis of their ratings of pain intensity, participants were categorized as having a low-pain or high-pain phenotype. Analyses revealed that children in the high-pain group were younger, more active, and scored higher in both state and trait anxiety. In addition, the authors examined alleles in 3 candidate genes in a pain pathway influenced by topical anesthetics: endothelin 1 (EDN1), endothelin receptor A (EDNRA), and endothelin receptor B (EDNRB). The EDNRA TT genotype was found to be significantly more prevalent in children in the high-pain group than those in the low-pain group. This type of research suggests that it may be possible in the future to match analgesic or anesthetic agents to specific patient characteristics, including their genotypes.

Relationships between the response to experimentally induced pain and gender, genetics (alleles of the vanilloid receptor subtype 1 gene [TRPV1], 8 opioid receptor subtype 1 gene [OPRD1], and catechol-O-methyltransferase gene [COMT]), temperament, and ethnicity have been demonstrated in adults. Thus, TRPV1 and OPRD1 alleles defined by single-nucleotide polymorphisms seemed to contribute to individual variation in thermal and cold pain sensitivity in association with effects contributed by gender, ethnicity, and temperament. Although additional research is needed, it seems that the relationship between pain responsiveness and temperamental variables as related to pain reactivity is particularly strong.

It is obvious that an individual’s genetic endowment for pain responsiveness is not likely to be altered. However, the possibility that a person might be assessed for these elements in clinical practice with an emphasis on pharmacogenetic and pharmacogenomic approaches may not be that far off. In the interim, the fact that some individuals may be far more sensitive to specific pain stimuli than others must always be considered, suggesting flexibility in the approach to pain management.

**Temperament**

Temperament refers to unique, relatively stable, genetically based behavioral traits that appear early in life. Elements of temperament set the stage for an individual’s basic responses to the environment (eg, one’s level of arousability) and, thus, set the stage for the development of important constructs such as personality traits, coping strategies, perception, and responsiveness to various stimuli including pain.

Bournaki studied 94 children between the ages of 8 and 12 years who underwent venipuncture during clinic visits and assessed elements of the child’s temperament (distractibility, intensity, and sensory threshold). The children’s general and medical-related fears, self-reported pain, observed behavioral distress, and heart rate were monitored. Canonical correlation revealed 2 variates. The first variate showed that with increasing age and in children with a high sensory threshold, fewer words were used to describe pain, fewer behavioral responses were manifested, and a lower magnitude of change in heart rate was observed. Findings from the second variate suggested that younger, highly fearful, distractible, and sensitive children reported higher pain quality and had increased heart rate reactivity. In addition to the insights gleaned regarding temperament and subjective and behavioral pain responses in this age group, Bournaki also noted that the findings supported the need for implementation of interventions in young children both before and during such relatively brief and simple medical procedures as venipuncture.

Broome et al conducted a 5-month longitudinal study that focused on children 4 to 18 years of age who were undergoing repeated lumbar punctures as part of their cancer treatment. Although pain reports decreased over time, their behavioral response to distress did not. Dimensions of temperament (including more-positive mood, lower activity, less persistence, and lower distractibility) measured at baseline were related to higher pain reports but not to behavioral distress. At the later time points, however, only the effect of positive mood persisted, suggesting that the influence of temperament may be modulated by other contextual elements.

Rocha et al investigated pain reactivity associated with inoculation in 5-year-old children. Children with temperaments characterized as low in adjustment (negative mood, unadaptable, withdrawn) exhibited enhanced pain reactivity. In addition, children who had more negative experiences with previous medical procedures reacted more intensely to inoculation pain than those with fewer negative experiences. It is interesting to note that the quality of the previous experience with medical procedures was more significant than the quantity.

Pain response to immunization at 4 or 6 months of age was evaluated by Piira et al by using a model that separated distal from proximal influences on pain. The former are variables deemed to have a less-direct impact on the experience, including gender, gestational and current age, temperament, and early experience with nociception, whereas the latter focus on immediate influences such as parental and nurse coping-promoting statements in the treatment room. In contrast to previous studies in which temperament was found to be fairly central, only age at immunization and gender were significant distal influences, whereas parental coping-promoting statements were the only significant proximal influence in predicting the duration of an infant’s cry.

Beyond procedural distress, there is evidence that the relationship between temperament and pain experiences is long-lasting. For example, Conte et al compared temperamental and stress response in 3 groups of patients: (1) children and adolescents with fibromyalgia; (2) children and adolescents with arthritis; and (3) healthy controls. Children and adolescents with fibromyalgia demonstrated more temperamental instability (lower mood, irregularity of daily habits, lower task orientation, and higher distractibility) and higher perceptual sensitivity, more symptom reporting, and greater total pain sensitivity compared with those in the other 2 treatment arms. Thus, predispositions associated with certain temperamental styles seem to set the stage for pain responses across a variety of contexts, from acute painful stimuli to long-term chronic pain problems.
As is the case with genetic endowment, an individual’s basic temperament is not likely to be changed very easily. The manner in which environmental elements interact with temperamental factors to affect coping and pain responses, however, is of great importance.

Coping
In addition to affecting sensitivity to pain stimuli, temperament also seems to play a significant role in coping with pain. Coping is the ability to deal with threatening, challenging, or potentially harmful situations. Individual coping strategies can be behavioral, including overt physical or verbal activities, or be more cognitive in nature, involving manipulation of thoughts and emotions. In general, coping strategies may involve blunting or avoidance, such as diverting attention away from the stressor, or may involve sensitizing or approach, including strategies for information seeking or close monitoring of the stressor. Some individuals combine these coping strategies at various points in time, and there is no clear pattern that is consistently superior in promoting adaptation to distress associated with medical procedures.

Wachs provided a comprehensive summary of the relationship between temperament and coping. Certain temperament traits, such as impulsivity, inhibition, and negative emotionality, seem to serve as developmental risk factors, whereas traits such as flexible self-regulation, sociability, and task orientation may enhance resilience. Five potential mechanisms for these relationships were described: (1) parents, other caregivers, and teachers provide differential treatment to children depending on their type of temperament; (2) children with different temperament styles seek out environments that may increase their risk or promote resilience; (3) the goodness (or poorness) of fit between a child’s temperament and environmental demand affect coping behavior; (4) children with different temperaments react to similar levels or types of stress in a variety of ways; and (5) children with different temperaments rely on different coping strategies. Certainly some of the aforementioned discrepancies in the precise role of temperament in pain responses may be explained on the basis of the specific mechanisms that are involved. However, most research studies have not examined these effects specifically to help guide our assessments and interventions.

Memory
Children’s memories of painful experiences can shape their future reactions to painful events. Such adaptations as habituation and sensitization emerge, and individual differences related to elements of temperament are important. In younger children, memory can often be distorted and contribute to negative perceptions of medical care. Memory of past interactions that involved pain can trigger anticipatory anxiety, thereby heightening a child’s pain response. A laboratory-based study of children aged 8 to 18 years who completed a measure of anxiety sensitivity before undergoing pain tasks (involving thermal, pressure, or cold stimuli) demonstrated that anticipatory anxiety contributed to more than one third of the variance in pain reporting across all tasks.

PERIPHERAL VENOUS ACCESS PROCEDURES
Cummings et al. examined the prevalence of pain and the major sources of pain in ~200 children admitted to a pediatric hospital. The insertion of IV lines was ranked along with disease-related pain and postoperative pain as 1 of the most common sources of significant pain. In another study, trained observers evaluated distress in 223 children and adolescents who were undergoing venipuncture without premedication or other interventions before the procedure. With a standardized 5-point observational distress scale (1, calm; 2, timid/nervous; 3, serious distress but still under control; 4, serious distress with loss of control; and 5, panic), high levels of distress (≥3 points) during the venipuncture were reported in ~50% of the children. When distress was evaluated according to age group, high levels were reported in 83% of the toddlers (2 years of age), 51% of preadolescents (7–12 years of age), and 28% of adolescents (≥12 years of age).

The pain and distress associated with venous access procedures may have far-reaching effects that include conditioned anxiety responses, increased pain perception, diminished analgesic effectiveness with subsequent procedures, and an avoidance of medical care because of blood-injection-injury phobia. Immediate effects of pain and distress during venous access procedures are also associated with negative consequences such as unsuccessful procedural attempts and lack of cooperation from a child, leading to increased time spent on performing the procedure. To understand how our current care system may initiate and reinforce difficulties in this setting, the findings that follow should be considered.

In classical conditioning models, a neutral stimulus is paired with a noxious stimulus, subsequently rendering the former stimulus noxious by itself. Clear evidence of such pain responses may be observed in the NICU, where premature infants typically undergo multiple (5–15) invasive procedures per day. A common painful experience in this setting is the heel lance, in which an infant’s leg is held, the heel is lanced with a blade, and blood is squeezed for collection and analysis. Data show that an increase in physiologic arousal indicative of a stress response occurs in such infants simply by lifting the infant’s foot. Thus, a response classically conditioned by pain is evident even at a very young age.

Unfortunately, the cycle may then be reinforced. Thurgate and Heppell noted that with advances in medical technology, more children are undergoing venipuncture as part of the diagnostic process. Children may need to be restrained when undergoing venous access procedures, particularly with inadequate preparation and inappropriate use of topical anesthetics, thus resulting in negative experiences and memories. On the basis of a conditioning model, when a child is exposed to or anticipates a needle insertion, anxiety or stress responses (crying, psychomotor agitation, freezing, or clinging) will be observed. Such arousal of the sympathetic nervous system and the adrenal medulla involves
an increase in heart rate and blood pressure and, problematically, vasoconstriction of the blood vessels that supply the skin. This, of course, makes venipuncture procedures much more difficult to perform, which reinforces the fear response even more, perhaps to the point of a frank needle phobia.

It is not surprising, therefore, that avoidance of needles persists well beyond the early years of childhood. In a study of 400 young adults who were visiting a clinic for travel immunizations, 21.7% indicated that they were afraid of injections, with that fear being unreasonably intense in 8.2% of the intended travelers. Hamilton stated that at least 10% of the population has a significant fear of needles, which often leads to avoidance in seeking medical care. Of course, estimates of the prevalence of those who truly avoid medical care are likely to be low because, by definition, those people are not available to be counted.

**SUMMARY: IMPROVING THE PEDIATRIC PAIN EXPERIENCE**

The aforementioned studies have made it clear that, even in very young children, pain, stress, and anxiety responses are associated with invasive procedures, including needle sticks. Failure to treat procedural pain and distress is harmful to children in 2 major ways. First, the child experiences unnecessary suffering during the procedure itself. Second, there may be long-term consequences including lasting changes in pain systems and pain responses that could have deleterious effects for years to come. It is no longer ethically justifiable or acceptable to ignore or downplay these issues. Besides the desire to be more humane in the treatment of our children, if poor management of early pain experiences clearly places a child at risk for future difficulties, because of either physiologic or psychological changes, the ethical imperative of “do no harm” is violated and, therefore, the clinical practice must be deemed unacceptable.

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*Pediatrics* 2008;122:S125
DOI: 10.1542/peds.2008-1055D

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