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Neonatal pain, parenting stress and interaction, in relation to cognitive and motor development at 8 and 18 months in preterm infants

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ABSTRACT

Procedural pain in the neonatal intensive care unit triggers a cascade of physiological, behavioral and hormonal disruptions which may contribute to altered neurodevelopment in infants born very preterm, who undergo prolonged hospitalization at a time of physiological immaturity and rapid brain development. The aim of this study was to examine relationships between cumulative procedural pain (number of skin-breaking procedures from birth to term, adjusted for early illness severity and overall intravenous morphine exposure), and later cognitive, motor abilities and behavior in very preterm infants at 8 and 18 months corrected chronological age (CCA), and further, to evaluate the extent to which parenting factors modulate these relationships over time. Participants were $N = 211$ infants ($n = 137$ born preterm $\leqslant$32 weeks gestational age [GA] and $n = 74$ full-term controls) followed prospectively since birth. Infants with significant neonatal brain injury (periventricular leucomalacia, grade 3 or 4 intraventricular hemorrhage) and/or major sensori-neural impairments, were excluded. Poorer cognition and motor function were associated with higher number of skin-breaking procedures, independent of early illness severity, overall intravenous morphine, and exposure to postnatal steroids. The number of skin-breaking procedures as a marker of neonatal pain was closely related to days on mechanical ventilation. In general, greater overall exposure to intravenous morphine was associated with poorer motor development at 8 months, but not at 18 months CCA, however, specific protocols for morphine administration were not evaluated. Lower parenting stress modulated effects of neonatal pain, only on cognitive outcome at 18 months.

1. Introduction

Early repeated procedural pain exposure in the neonatal intensive care unit (NICU) has been proposed as one of the factors that may contribute to altered development of cognition, motor function and behavior in infants and children born preterm [2,22,26], although this link has been largely speculative. Neurobiological vulnerability to pain in preterm infants is well established, due to their lower pain threshold, sensitization from repeated pain [16,17], and immature systems for maintaining homeostasis. The physiological perturbations associated with early prolonged exposure to episodic pain appear to contribute to altering the rapidly developing stress systems [24,28]. Nociceptive signals during neonatal blood collection reach the cortex [8,44], and in rat pups, neonatal inflammatory pain may affect the cytoarchitecture of the brain [3].

Due to plasticity of the immature nervous system, long-term effects of early exposure to negative environments may be at least partially ameliorated by positive child-rearing environment [13]. Moreover, effects of neonatal pain on stress systems appear to be prevented by increased maternal behaviors in rodents [45]. In human infants, caregiver interaction and family social context are important modulators of neurodevelopment in infants born preterm, with increasing importance of the socioeconomic and family environment over time [40].

The aims of the present study were to evaluate whether cumulative neonatal procedural pain in very preterm infants is associated with altered cognitive and/or motor neurodevelopment at age 8 and 18 months corrected chronological age (CCA; i.e. adjusted for prematurity), and whether environmental context of parenting stress and parent–infant interaction buffers effects of neonatal pain on neurodevelopment. As a comparison group for

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neurodevelopment and parent factors, we included a sample of infants born full-term.

Major neurodevelopmental impairments such as cerebral palsy appear to be influenced by other factors, such as intrauterine infection and severe neonatal brain injury [19,41]. Therefore to avoid confounders of effects of neonatal pain, we excluded infants who had major brain injury on neonatal ultrasound or major neurosensory impairments. Therefore this study addressed associations between neonatal procedural pain and neurodevelopmental outcomes in relatively intact infants born very preterm. To our knowledge, this is the first study to examine pain in relation to neurodevelopment in preterm infants past the neonatal period.

2. Methods

2.1. Participants

As part of a larger longitudinal project, $N = 211$ (137 preterm, 74 full-term) infants completed the Bayley Scales of Infant Development-II ([9] Bayley, 1993) at 8 and/or 18 months CCA, and a parent participated in mother–infant interaction play and completed a questionnaire on parenting stress. Infants with a major congenital anomaly, major neurosensory impairment (legally blind, cerebral palsy, sensori-neural hearing impairment), severe brain injury evident on neonatal ultrasound (periventricular leucomalacia or grade 3 or 4 intraventricular hemorrhage), or maternal report of illicit hard drugs during pregnancy, were excluded. The children seen at the 8 month visit only (116 preterm, 69 full-term) or at the 18 month visit only (102 preterm, 55 full-term) did not differ significantly in birth weight, gestational age, Bayley cognitive or motor scores from the children seen at both 8 and 18 months CCA (82 preterm, 50 full-term).

The preterm infants were born in February 2001–September 2004, and were recruited from the neonatal intensive care unit (NICU) at the Children's and Women's (C&W) Health Centre of British Columbia, which is the major tertiary neonatal unit for the province of British Columbia, Canada. Full-term infants were born in May 2001–July 2004 at the same Centre, and were contacted through their pediatricians. Developmental assessments were carried out at age 8 and 18 months CCA blinded to the infant's pain history and family data. Infant neonatal characteristics and demographic factors with data at one or both ages are shown in Table 1. As expected, the preterm infants had lower gestational age ($F[1,203] = 1086.95$, $p = .0001$), and birth weight ($F[1,203] = 1009.96$, $p = .0001$). Mothers of the preterm infants had lower number of years of education ($F[1,203] = 23.59$, $p = .0001$).

2.2. Measures

2.2.1. Medical chart review

Medical and nursing chart review from birth to term (39 weeks 6 days) was carried out by one neonatal research nurse, including but not limited to birth weight, gestational age, illness severity (SNAP-II) on day 1, days of mechanical ventilation, daily dosage of intravenous (iv) morphine and other medications, and number of skin-breaking procedures (e.g. heel lance, intramuscular injection, chest tube insertion, central line insertion). Procedural pain exposure was operationalized as the sum of every skin-breaking procedure from birth to term, adjusted for early illness severity (SNAP-II on day 1) and iv morphine exposure. Each attempt at a procedure was included, thus the total sum reflected all skin breaks. While it is recognized that procedures differ in pain intensity, in the absence of an empirical basis for assigning weights to every procedure, we count every skin break as a "marker" of cumulative neonatal acute pain exposure in the NICU [e.g. 24,25,27,28]. Total morphine exposure was calculated from birth to term as the average daily dose of iv morphine adjusted for daily weight, multiplied by the number of days on morphine, as we have used previously. For example, if an infant received an average dose of 0.39 mg/kg body weight for 24 treatment days, the morphine score was 9.36 [mg/kg]. All nursing staff in our NICU have been trained to carry out very precise recordings of every skin-breaking procedure, including each attempt, therefore we have highly consistent chart information on every infant.

2.2.2. Neurodevelopment

The Bayley Scales of Infant Development 2nd Edition [9], the most widely used standardized tests of infant and toddler development, were administered at 8 and 18 months CCA. The Mental Development Index (MDI) measures cognitive and language function and includes eye-hand items such as stacking blocks, as well as concrete problem solving tasks, and receptive and expressive vocabulary items; the Psychomotor Development Index (PDI) primarily includes items measuring gross motor development. The MDI and PDI each has a mean of 100 and SD of 15. .

2.2.3. Questionnaires

We measured parenting stress using the Parenting Stress Index [1], a 120 item questionnaire, with each item on a 6-point Likert scale from 1 (strongly agree) to 6 (strongly disagree); Cronbach's alpha was .91 for the Total Stress score. Demographic Information: was obtained by questionnaire. Since maternal education is the single most important socioeconomic status (SES) indicator related

Table 1
Infant neonatal and demographic characteristics.

Characteristics	Preterm $n = 137$	Full-term $n = 74$	p-Value
Gestational age at birth (weeks) mean (SD)	29.1 (2.6)	40.0 (1.1)	.0001
Birth weight (grams) mean (SD)	1263.1 (485.6)	3534.8 (488.9)	.0001
Illness severity day 1 (SNAP-II) mean (SD)	13.1 (12.2)	n/a	n/a
Skin- breaking procedures (number)* mean (SD)	121.1 (99.6)	n/a	n/a
Mechanical ventilation (days)* mean (SD)	13.8 (21.4)	n/a	n/a
IV morphine exposure (daily average mg/kg × days)* mean (SD)	2.7 (6.8)	n/a	n/a
Postnatal dexamethasone (days)* mean (SD)	1.5 (6.0)	n/a	n/a
Birth weight small-for-gestational-age (%)	13	3	.06
Sex (% male)	48	48	1.00
Number of children in the home mean (SD)	1.9 (1.0)	1.7 (0.7)	.18
Mother's years of education (years) mean (SD)	14.9 (2.8)	16.9 (2.9)	.0001
Mother completed high school or above (%)	92	98	.11
Marital status (% married or common-law)	77	85	.31
Ethnicity of mother (% Caucasian)	72	78	.21

* Recorded daily from birth to term (40 weeks post-conceptional age).