Neurobehavioral Assessment Predicts Motor Outcome in Preterm Infants

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Objective To determine whether Neonatal Intensive Care Unit Network Neurobehavior Scales (NNNS) at 44 weeks predict motor outcome at 2 years in preterm infants from the Maternal Lifestyles Study (MLS).

Study design Data were collected on all preterm infants (<36 weeks) in the MLS who underwent an NNNS at 44 weeks (n = 395) and neurologic examination at 12 to 36 months or Bayley Psychomotor Development Index (PDI) at 24 months (n = 270). Logistic regression analyzed NNNS summary scores associated with cerebral palsy (CP) or PDI <70, while controlling for birth weight ≤1250 g.

Results Eighteen of 395 infants (5%) had CP; 24 of 270 infants (9%) had PDI <70. CP was associated with low quality of movement (odds ratio [OR], 1.95; 95% CI, 1.24-3.06; P = .004) and high lethargy (OR, 1.67; 95% CI, 1.01-2.76; P = .045). The model contributed 19% of the variance in CP diagnosis at 12 to 36 months (R^2 = .19, P < .001). Low PDI was associated with low handling (OR, 1.83; 95% CI, 1.12-2.99; P = .017), low quality of movement (OR, 2.16; 95% CI, 1.38-3.38; P = .001), and hypotonia (OR, 1.63; 95% CI, 1.14-2.32; P = .007). The model contributed 26% of the variance in PDI <70 at 24 months (R^2 = 0.26, P < .001).

Conclusions The neurobehavioral profile of under-arousal in 44-week-old preterm infants may predict poor motor outcome. *(J Pediatr 2010;156:366-71)*.

See editorial, p 347 and related article, p 359

Although the survival rate of extremely low birth weight (ELBW) infants is steadily improving, the incidence of disability in this patient population remains high.[1] Cerebral palsy (CP) develops in approximately 12% to 21% of ELBW infants,[1-5] and 29% to 40% have Bayley Psychomotor Developmental Index (PDI) scores< 70 (<2 SD below the mean) at 18 months corrected age (CA).[2,4] These infants require multiple supports and interventions, including physical and occupational therapy.[6] Although multiple studies in the past 2 decades have identified some risk factors for poor motor outcome in this population,[2,5,7-13] no reliable predictor has been identified.

Perhaps the most important predictor of CP or low motor score is the finding of abnormalities on neonatal cranial ultrasound scanning. Multiple authors have reported a 2- to 6-fold increased risk of CP associated with grade 3 to 4 intraventricular hemorrhage (IVH)[5,10-14] and a 3- to 10-fold increased risk of CP associated with cystic periventricular leukomalacia (PVL).[5,10,11,14] The presence of hydrocephalus may increase the risk by 12.2 times,[12] and the presence of PVL and hydrocephalus may increase the risk by 15.4 times.[14] According to results from the Indomethacin trial, 60% of ELBW infants with grade 3 to 4 IVH had CP at 5 years of age and 92% required special services.[15]

However, ultrasound scanning, although helpful, lacks both sensitivity and specificity. IVH grade has been shown to account for only 5% of the variance in predicting major handicap and 4% of the variance in predicting low PDI score.[8] Additionally, 6% to 9% of ELBW infants who demonstrate no abnormalities on cranial ultrasound scanning have CP at 18 to 22 months CA.[7,16] Magnetic resonance imaging (MRI) may be more predictive of neurodevelopmental outcomes in preterm infants than cranial ultrasound scanning.[17,18] Although MRI identifies more subtle white matter lesions than cranial ultrasound scanning, it remains controversial whether MRI is superior in predicting outcomes.[19-22] In addition, MRI is expensive and impractical, requiring transportation and often sedation of the infant. Thus identification of those infants in whom neurodevelopmental impairment will develop and who may benefit from intervention services remains flawed.

BPD	Bronchopulmonary dysplasia	NBAS	Neonatal Behavioral Assessment Scale
BSID-II	Bayley Scales of Infant Development, 2nd edition	NNNS	Neonatal Intensive Care Unit Network Neurobehavior Scales
CA	Corrected age	OR	Odds ratio
CP	Cerebral palsy	PCA	Post-conceptional age
ELBW	Extremely low birth weight	PDI	Psychomotor Development Index
IVH	Intraventricular hemorrhage	PVL	Periventricular leukomalacia
MLS	Maternal Lifestyles Study	SGA	Small for gestational age
MRI	Magnetic resonance imaging		
NAPI	Neurobehavioral Assessment of the Preterm Infant		

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Neurologic or neurobehavioral assessment may be a more accurate way to predict outcome in ELBW infants.[23-25] The Neonatal Intensive Care Unit Network Neurobehavioral Scale (NNNS)[26] is a standardized neurobehavioral assessment of the high-risk neonate. The NNNS summary scale is significantly correlated with the Bayley[27] PDI at 12 months CA, and specific NNNS motor function scores are significantly correlated with motor scales performed at 4 and 18 months in term neonates.[28] Preterm infants perform differently than term infants on most NNNS summary scores.[29] In preterm infants (≤30 weeks gestation), NNNS scores correlate with white matter abnormalities on MRI and may correlate with motor outcomes.[30] No conclusive data exist correlating NNNS summary scores and future motor development in preterm infants.

The purpose of this study was to determine the relationship between NNNS summary scores at 44 weeks post-conceptional age (PCA) and CP at 12 to 36 months or low PDI at 24 months, in a cohort of infants born <36 weeks gestation and enrolled in the Maternal Lifestyles Study (MLS), a study evaluating the impact of maternal lifestyle during pregnancy on childhood outcome. We hypothesized that some NNNS summary scores from infants examined at 44 weeks PCA would be independently associated with the findings of CP at 12 to 36 months or low PDI at 24 months in infants born <36 weeks from the MLS.

Methods

We analyzed data collected on all infants in the MLS who were born preterm (<36 weeks gestation) and had an NNNS performed at 44 weeks PCA (n = 395) and a neurologic examination at 12 to 36 months CA, Bayley Scales of Infant Development at 24 months CA (n = 270), or both.

The NNNS[26] was originally developed for the Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network MLS. It has been used extensively to evaluate infants with a history of in utero substance exposure, and NNNS scores have been related to prenatal drug exposure, including cocaine,[31,32] methamphetamine,[31,33] marijuana,[34] and tobacco,[35,36] in term and preterm infants.[29] The NNNS was designed to provide a comprehensive assessment of neurologic integrity, behavioral functioning, and stress behavior. It has been validated in large groups of term and preterm infants. The neurologic examination includes assessment of active and passive tone, primitive reflexes, and items that assess the integrity of the central nervous system and maturity of the infant. The behavioral component is based on the Neonatal Behavioral Assessment Scale (NBAS)[37] and includes assessment of state, sensory, and interactive responses. The stress component is a checklist of observations based on the work of Finnegan.[38]

The NNNS follows a fixed sequence of administration that starts with a pre-examination observation, followed by the neurologic and behavioral components. The stress/abstinence scale is based on signs of stress observed throughout the examination. The NNNS items are scored with these 13 summary scores: habituation, attention, arousal, regulation, number of handling procedures, quality of movement, excitability, lethargy, number of nonoptimal reflexes, number of asymmetric reflexes, hypertonicity, hypotonicity, and stress/abstinence signs. Psychometric properties of the summary scales were evaluated with coefficient alphas ranging from 0.56 to 0.85.

The MLS is the largest clinical, prospective, longitudinal study to date of acute neonatal events and long-term health and developmental outcomes associated with cocaine use during pregnancy.[31,39] Enrollment and exclusion criteria for the MLS have been described in detail in earlier publications.[31,39] The MLS was approved by the institutional review board at each study site, and written informed consent was obtained for enrollment of each infant. Infants enrolled in the longitudinal phase of MLS were selected for the longitudinal phase to be in the exposed group (maternal report of cocaine or opiate use during pregnancy or gas chromatography-mass spectrometry confirmation of presumptive positive screens for cocaine or opiate metabolites) or the comparison group (maternal denial of cocaine or opiate use during the pregnancy and a negative results on an enzyme multiplied immunoassay technique screen for cocaine and opiate metabolites). Exposed infants and comparison infants were matched for race, sex, and gestational age. The 1388 mother-infant dyads (658 in the exposed group and 730 in the comparison group) that came to the 1-month visit were enrolled in the longitudinal study. All 1388 infants were examined between 42 and 44 weeks PCA by psychometrists certified on the NNNS examination and masked as to infant exposure status. The NNNS was completed in 1211 of these infants. Infants were then seen at 12, 24, and 36 months follow-up. At each visit, a nurse administered a questionnaire to the caregiver to update the infant's medical history since the last visit, and infants underwent a neurologic examination performed by physicians and nurses trained in the diagnosis of CP who were blinded to the infant's perinatal history and exposure status. Examiners administered the mental and motor scales of the Bayley Scales of Infant Development, 2nd edition (BSID-II) at 24 months of age.[40] Examiners were certified annually in their administration and scoring of these examinations.

Of the 1388 infants enrolled in the longitudinal phase of MLS, 454 were preterm (<36 weeks). A total of 395 of these

Table I. Infant characteristics

	Mean	SD	Range
Birth weight, g	1782	± 618	519-3390
Length, cm (at birth)	42	± 5	28-53
Head circumference, cm (at birth)	29	± 3	21-36
Gestational age	31.5	± 3.3	21-35
1-minute Apgar	7	± 2.2	0-9
5-minute Apgar	8	± 1.3	1-10
Male	49%		
Birth weight ≤1250 g	22%		
SGA	18%		
Intrauterine drug exposure	45%		
MDI at 18 months	80	± 14	49-146
PDI at 18 months	92	± 16	49-125