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Neurobehavioral Assessment Predicts Motor Outcome in Preterm Infants

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Abstract

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 had an NNNS at 44 weeks (n=395) and neurologic exam at 12–36 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 1250g.

Results—Eighteen of 395 infants (5%) had CP; 24 of 270 infants (9%) had PDI <70. CP was associated with low quality of movement (OR 1.95, 95% CI 1.24–3.06, p=0.004) and high lethargy (OR 1.67, 95% CI 1.01–2.76, p=0.045). The model contributed 19% of the variance in CP diagnosis at 12–36 months ($R^2=0.19$, p<0.001). Low PDI was associated with low handling (OR 1.83; 95% CI 1.12–2.99, p=0.017), low quality of movement (OR 2.16; 95% CI 1.38–3.38, p=0.001), and hypotonia (OR 1.63; 95% CI 1.14–2.32, p=0.007). The model contributed 26% of the variance in PDI <70 at 24 months ($R^2=0.26$, p<0.001).

Conclusions—The neurobehavioral profile of underarousal in 44 week preterm infants may predict poor motor outcome.

Keywords

neurobehavior; outcomes; ELBW

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 Approximately 12–21 percent develop cerebral palsy (CP)^{1–5} and 29–40% have Bayley Psychomotor Developmental Index (PDI) scores < 70 (< 2 standard deviations below the mean) at 18 months corrected age (CA).^{2, 4} These infants require multiple supports and

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interventions including physical and occupational therapy.⁶ Though multiple studies over the past two 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. Multiple authors have reported a 2 to 6 fold increased risk of CP associated with Grade 3–4 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 by 15.4 times.¹⁴ According to results from the Indomethacin trial, 60% of ELBW infants with grade 3–4 IVH had CP at 5 years of age and 92% required special services.¹⁵

Yet ultrasound, although helpful, lacks both sensitivity and specificity. In fact 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, 6–9% of ELBW infants who demonstrate no abnormalities on cranial ultrasound have CP at 18–22 months CA.^{7, 16} Magnetic resonance imaging (MRI) may be more predictive of neurodevelopmental outcomes in preterm infants than cranial ultrasound.^{17, 18} Even though MRI identifies more subtle white matter lesions than cranial ultrasound, 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 individual infants who will develop neurodevelopmental impairment and may benefit from intervention services remains flawed.

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 Bayley²⁷ 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 Scores²⁹ and 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 exists 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 postconceptional age (PCA) and CP at 12–36 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 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 12–36 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 born preterm (< 36 weeks gestation) who had an NNNS performed at 44 weeks PCA ($n=395$) and a neurologic exam at 12–36 months CA and/or Bayley Scales of Infant Development at 24 months CA ($n=270$).

The Neonatal Intensive Care Unit Network Neurobehavioral Scale (NNNS)²⁶ was originally developed for the Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network Maternal Lifestyles Study (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} marijuana³⁴ and tobacco,^{35, 36} in term and preterm infants²⁹ The NNNNS 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 NNNNS follows a fixed sequence of administration that starts with a preexamination observation, followed by the neurologic and behavioral components. The stress/abstinence scale is based on signs of stress observed throughout the examination. The NNNNS items are scored using the following 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 .56 to .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 previous publications.^{31, 39} The MLS study 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 enzyme multiplied immunoassay technique screen for cocaine and opiate metabolites). Exposed infants and comparison infants were matched on 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' postconceptional age by psychometrists certified on the NNNNS examination and masked as to infant exposure status. The NNNNS was completed on 1211 of these infants. Infants were then seen at 12, 24 and 36 month 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 exam 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). 395 of these preterm infants had an NNNNS completed at 44 weeks, and 270 participated in a BSID-II 24 months of age. Age of administration was corrected for prematurity.

Step forward logistic regression analyses were performed to examine the association between NNNNS summary scores and outcome (CP at 12–36 months or PDI <70 at 24 months), while controlling for birth weight 1250g. All of the NNNNS summary scores were normalized as z scores before entered into the model because of the large differences in

scales and variances among these summary scores. The final model included only those variables significantly related to outcome. Criteria for entry into the model were $p < 0.05$. Separate models were run for each outcome, one with and one without birth weight.

RESULTS

The cohort of 395 infants had a mean birth weight of 1782 (± 618) grams (range 519–3390) and mean gestational age was 31.5 (± 3.3) weeks (range 21–35) (Table I). About half ($N = 195$, 49.4%) were male and half (179, 45.3%) were exposed to cocaine in utero. Of the 395 infants in the cohort, 85 (22%) had a birth weight 1250g and 70 (18%) were born small for gestational age (SGA).

The majority of the mothers in this cohort (81%) was African-American, had only completed a high school education (60%), was Medicaid insured (81%), and was living below the poverty level (62%) (Table II). Infant and maternal characteristics of the subset of 270 infants seen at 2 years were similar to the characteristics of the entire cohort of 395.

Of the 395 infants who returned for a neurologic exam between 12 and 36 months of age, 18 (5%) were diagnosed with cerebral palsy. Of the 270 who returned at 24 months for a BSID-II, 24 (9%) had a PDI score < 70 (> 2 standard deviations below the mean) which was consistent with severe delays in motor development.

The 4 step forward logistic regression models run to predict CP and PDI < 70 are shown in Tables III and IV. Table III depicts the models run to predict CP or PDI < 70 without the addition of birth weight. Table IV depicts the models run to predict CP or PDI < 70 while controlling for birth weight. Three NNNS Summary Scores, low Handling score, low Movement score, and high Lethargy score, were significantly related to CP diagnosis (Table III) Each variable had an associated 2 fold increase in the risk of CP at 12–36 months. This model accounts for 14% of the variance in diagnosis of CP. When birth weight was entered into the model (Table IV), only low Movement score and high Lethargy score remained significant predictors of CP. As expected, birth weight was associated with a 5.5 fold increased rate of CP. This model accounts for 19% of the variance in CP.

Tables III and IV also depict the step forward logistic regression models to predict PDI < 70 at 24 months. Low Handling score, low Movement score, Hypotonia and high State Stress score were each associated with low PDI at 24 months (Table III). This model accounts for 19% of the variance in low PDI score. However, when birth weight was entered into the model (Table IV), only low Handling score, low Movement score, and Hypotonia remained significant predictors of low PDI score. Birth weight also resulted in an almost 6 fold increased rate of low PDI score. This model accounts for 26% of the variance in low PDI score.

DISCUSSION

In these models, 19% of the variance in CP at 12–36 months and 26% of the variance in low PDI at 24 months is explained by specific NNNS summary scores and low birth weight. A combination of NNNS summary scores explains 2–3 times more of the variance in motor outcome than low birth weight.

Multiple investigators have attempted to identify predictors for CP and poor motor outcome in preterm infants. Low birth weight has been identified as perhaps the most important contributor to neurologic and motor outcomes in multiple previous publications. Other factors associated with poor motor outcomes include sociodemographic (maternal education $< 12^{\text{th}}$ grade, ^{5, 8, 10} Medicaid enrollment¹¹), biologic (male sex, plurality, low birth

weight),^{5, 7, 10} perinatal (prolonged premature rupture of membranes, maternal bleeding, chorioamnionitis, delivery at a hospital with a Level 1 nursery only),¹³ neonatal (5 minute Apgar,^{5, 12} bronchopulmonary dysplasia (BPD),^{2, 5, 7–12} postnatal Steroids,^{2, 5, 10, 11} necrotizing enterocolitis,² infection,^{5, 13} pneumothorax,^{7, 13} seizures,¹³ hydrocephalus¹²).

Though risk factors for poor neurologic outcome have been identified, attempts to predict neurologic morbidity based on identifiable risk factors has proven largely unsuccessful. Several investigators have used univariate and/or multiple logistic regression analyses to identify a combination of important predictors for CP or poor motor outcome.^{4, 12, 13, 41} Ambalavanan used both regression analysis and neural networks to attempt to predict a Bayley PDI < 68 at 12–18 months corrected age using perinatal and neonatal characteristics. Less than 15% of the variance in low PDI was explained by IVH grade, PVL, BPD, chorioamnionitis, and low maternal education.⁸

Although abnormalities on neuroimaging are important in identifying infants at risk for abnormal neurologic outcomes in preterm infants, both cranial ultrasound and MRI are flawed in their predictive abilities.^{20–22} Evidence suggests that MRI is superior to ultrasound in identifying white matter abnormalities, but the significance of these findings is not clear. The largest study to date of MRI and neurodevelopmental impairment found that 22% of preterm infants with no or mild white matter injury on MRI at term equivalent have neurodevelopmental impairment at 2 years of age, and 50% of preterm infants with moderate to severe white matter injury at term equivalent have no neurodevelopmental impairment at 2 years.²²

Neurologic or neurobehavioral assessment has been studied as a potentially more accurate way to predict outcome in ELBW infants. In 1997 Prechtl reported high sensitivity (95%) and specificity (96%) of one hour of videotaped spontaneous movements in predicting 2 year neurologic outcome in a cohort of term and preterm infants with fidgety movements.²⁵ More recently, Garcia demonstrated less positive results.⁴² In their cohort of 40 preterm infants, 20 minute videotaped observations of gross motor movements varied in accuracy for predicting abnormal neurologic outcome by timing of exam (prior to 37 weeks adjusted age, 37–42 weeks adjusted age, and >42 weeks adjusted age). Sensitivity ranges from 75–100%, specificity from 44–67%, positive predictive value from 36–60% and negative predictive value from 80–100%.

Spittle et al described a significant correlation between videotaped assessments of general movements at 1 and 3 months post-term and white matter abnormalities on MRI at term equivalent,⁴³ but no data from neurologic follow-up of these infants was reported.

The Neurobehavioral Assessment of the Preterm Infant (NAPI) was used to predict outcome at 12, 18 and 30 months corrected age.^{23, 24} Infants who went on to diagnosis of CP had lower NAPI scores for alertness and orientation at 36 weeks but no difference in NAPI motor scores compared with infants without CP. The association between NAPI score and poor motor outcome as measured by low PDI score was not explored.

Several authors have described the neurobehavioral assessment of the preterm infant using various neurobehavioral assessment tools.^{44–49} Miller-Loncar et al described an association between NNNS summary scores, Bayley²⁷ PDI at 12 months and Motor scales performed at 4 and 18 months in term neonates.²⁸ Brown et al described significant differences in NNNS summary scores between term and preterm infants.²⁹ In an unpublished study of a small group of preterm infants NNNS scores were associated with white matter abnormalities on MRI and motor outcomes at 24 months.³⁰

This study demonstrated an association between neurobehavioral assessment using the NNNS and poor motor outcome at 24 months as defined by PDI <70 and /or CP in a large cohort of preterm infants. Specific summary scores were identified in these models as significant predictors of poor motor outcome (CP and /or low PDI) at 12–36 months. These summary scores, low movement, high lethargy, low handling, and hypotonia, describe an infant with significant underarousal.

As the original MLS Study was designed to look at the effects of prenatal cocaine exposure, a large number of infants in this study were exposed to cocaine (and other substances) in utero. It is not clear whether these results will generalize to all preterm infants, the majority of whom are not exposed to these substances in utero. In addition, our follow-up rate was low as only 68% of the infants in our cohort had a Bayley at 24 months. Thus further prospective work is needed to determine the predictive ability of the NNNS for all preterm infants.

Neonatal correlates to cerebral palsy have long been known and frequently involve a clinical picture of decreased tone and/or movement.⁵⁰ Thus the association between performance on the NNNS, a comprehensive assessment of neurologic integrity, behavioral functioning, and stress behavior, and cerebral palsy is not surprising. These findings imply that neurobehavioral assessment can and should be added to our assessment of risk for poor motor outcome in all preterm infants. Findings of underarousal on the NNNS at term equivalent provide additional information about the risk of poor motor outcome. The addition of these findings to those of chronic lung disease, intraventricular hemorrhage and periventricular leukomalacia will increase our ability to predict cerebral palsy and improve our ability to counsel families of preterm and low birth weight infants.

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Abbreviations

ELBW	Extremely low birth weight
CP	Cerebral palsy
PDI	Psychomotor development index
CA	Corrected age
IVH	Intraventricular hemorrhage
PVL	Periventricular leukomalacia
MRI	Magnetic resonance imaging
NNNS	Neonatal Intensive Care Unit Network Neurobehavioral Scale
PCA	Postconceptional age
MLS	Maternal Lifestyles Study
NBAS	Neonatal Behavioral Assessment Scale
BSID-II	Bayley Scales of Infant Development, 2 nd edition
SGA	Small for gestational age

BPD	Bronchopulmonary dysplasia
NAPI	Neurobehavioral Assessment of the Preterm Infant

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Table 1

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 ≤ 1250g	22%		
SGA	18%		
Intrauterine drug exposure	49%		
MDI at 18 months	80	± 14	49–146
PDI at 18 months	92	± 16	49–125

Table 2

Maternal Characteristics

Race	African-American	81% 1
	White	4%
	Hispanic	4%
	Other	1%
Age	18–25yr	35%
	26–35yr	52%
	36–49yr	13%
Education	High school	60%
Insurance	Medicaid	81%
	Private	19%
Prenatal care	None	19%
Hollingshead	Level 5 (low)	26%
Poverty level	<100%	62%

Table 3

Results of Logistic Regression to Predict Cerebral Palsy and PDI < 70 at 24 months

Outcome	Predictors	OR (95% CI)	P value	R-Square
CP Diagnosis	Low Handling	1.79 (1.05–3.05)	0.033	.14*
	Low Movement	2.00 (1.26–3.16)	0.003	
	High Lethargy	1.76 (1.12–2.81)	0.017	
PDI < 70	Low Handling	1.92 (1.19–3.10)	0.008	.19*
	Low Movement	1.72 (1.12–2.63)	0.013	
	Hypotonia	1.52 (1.08–2.15)	0.017	
	State Stress	1.67(1.004–2.78)	0.048	

* p-value for the model < 0.001

Table 4

Results of Logistic Regression to Predict Cerebral Palsy and PDI < 70 at 24 months with Birth Weight in the Model

Outcome	Predictors	OR (95% CI)	P value	R-Square
CP Diagnosis	Low Movement	1.95 (1.24–3.06)	0.004	.19*
	High Lethargy	1.67 (1.01–2.76)	0.045	
	Birth weight ≤1250g	5.49 (1.99–15.16)	0.001	
PDI < 70	Low Handling	1.83 (1.12–2.99)	0.017	.26*
	Low Movement	2.16 (1.38–3.38)	0.001	
	Hypotonia	1.63 (1.14–2.32)	0.007	
	Birth weight ≤1250g	5.97 (2.29–15.54)	<0.001	

* p-value for the model < 0.001