Neurobiologic Risk Score and Long-term Developmental Outcomes of Premature Infants, Birth Weight Less Than 1,250 Grams

PRACHA NUNTNARUMIT, M.D.*, HENRIETTA S. BADA, M.D.**,
SHELDON B. KORONES, M.D.**, WENJIAN YANG, Ph.D.***

Abstract

Objective : To determine whether neurobiologic risk score (NBRS) would continue to correlate with developmental outcomes.

Method : An observational cohort consisting of 258 surviving infants who returned to the follow-up clinic with a mean age 22 months' corrected age. Both univariate and multivariate analysis were performed to identify risk factors and to assess the predictive value of NBRS.

Results : Forty-eight to 53 per cent of these infants had growth parameters < 25th percentile for age. Seventeen and 18 per cent respectively had mental developmental index (MDI) and psychomotor developmental index (PDI) on the Bayley Scales less than 70 and 14 per cent developed cerebral palsy (CP). NBRS demonstrated a significant correlation with the outcome ($p<0.001$). In infants with NBRS ≥ 8, 48 per cent had MDI < 70 and 68 per cent, had PDI < 70. At a similar NBRS cut-off, specificity and negative predictive value (NPV) were 86 and 96 per cent, respectively. Logistic regression indicated that birth weight and gestational age were the most significant independent variables for predicting poor outcomes.

Conclusion : Very preterm infants in the present study were at risk for abnormal developmental outcomes. NBRS demonstrated a very high specificity and NPV and may be a useful index to identify those who need early intervention.

Key word : Developmental Outcome, Preterm Infant, Neurobiologic Risk Score

**NUNTNARUMIT P, BADA HS,
KORONES SB, YANG W
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* Department of Pediatrics, Faculty of Medicine, Ramathibodi Hospital, Mahidol University, Bangkok 10400, Thailand.
** Department of Pediatrics and Obstetrics and Gynecology, The University of Tennessee, Memphis, Tennessee, USA.
*** Department of Mathematical Science, The University of Memphis, Tennessee, USA.

Very premature infants are at the highest risk for abnormal development and in greatest need for early intervention. Many scoring systems have been developed in an attempt to define the relationship of perinatal events on subsequent outcomes and to identify those who would need close follow-up. One of the scoring systems is the Neurobiologic Risk Score (NBRS) which was described by Brazy et al[1] in 1991. These scores are based on neonatal events which are likely to cause irriversible brain damage resulting from hypoxia, ischemia, insufficient substrate for metabolism or direct damage to tissue and also emphasize the severity and duration of such events. From the initial report on infants with birth weight less than 1,500 grams, 13 items and/or events were selected for analysis and only 7 items, which included infection, blood pH, seizures, intraventricular hemorrhage, assisted ventilation, periventricular leukomalacia and hypoglycemia, showed significant correlation with findings from Bayley Scales of Infant Development and with abnormal neurological findings through 24 months' corrected age. The scoring system had a 100 per cent specificity and 100 per cent positive predictive value for abnormal outcomes using a cut point score of ≥ 6. However, the abnormal outcomes in their initial report were defined as a mental developmental index (MDI) or psychomotor developmental index (PDI) < 85 which included borderline mental or motor ability, not severe handicap or functional disability. Furthermore, in a subsequent study[2] conducted by the same investigators in a larger population with the similar birth weight, the neurobiologic risk score seemed to lose some of its power in predicting abnormal outcomes with relatively low sensitivity and positive predictive value; specificity and negative predictive value remained high. Although there is no clear evidence to show that early intervention would benefit all high risk infants, some studies have suggested that such an intervention for those infants with mental or physical dysfunction enhanced the ability of their limited potential in some areas of development[3-5]. It has been shown that not only biological risks influence developmental outcomes, but socioeconomic and environmental factors also have an increasing impact on later development as the predictive ability of biologic risks tend to decrease with increasing post natal age[6].

The objections of this study were to

1. determine the risk factors associated with moderate to severe developmental deficits in infants with a birth weight less than 1,250 grams.

2. determine whether NBRS would continue to correlate with developmental outcomes in a group of lower birth weight infants with a longer period of follow-up than previous studies. The authors hypothesized that NBRS will correlate with neurodevelopmental outcomes: high score would predict poor outcomes through three years corrected age.

METHOD

The observational cohort study was selected from a population consisting of infants with birth weight $\leq 1,250$ g, without major congenital anomalies or identifiable syndromes who were born at the Regional Medical Center, Memphis between January 1993 and December 1995 and were discharged alive. Documentation included prenatal history, nursery clinical course and complications. The NBRS was determined from chart data at the time of discharge from the intensive care nursery. The details for assessing and scoring the NBRS have been described previously[1,2]. The scoring system consisted of 7 perinatal related- items/events including duration of mechanical ventilation, pH value (metabolic or respiratory acidosis), convulsion, degree of intraventricular hemorrhage, presence and severity of periventricular leukomalacia, sepsis or meningitis and level and duration of hypoglycemia. Each item is graded 0,1,2, and 4 according to severity and duration. A total score of less than 5 was considered to be low risk, between 5 and 7 as intermediate risk, and a score ≥ 8 as high risk[2]. Infants were evaluated at 1, 4, 8, 12, 18, 24, 30, and 36 months' corrected age. Evaluations included physical and neurological examination, nutritional and growth assessment, visual and auditory screening and developmental assessment. The Bayley Scales of Infant Development edition II were administered by a psychologist and findings were expressed in terms of mental developmental index (MDI) indicating mental development and psychomotor developmental index (PDI) as indicator of motor performance. The Bayley scales II results used for analysis in this study were selected from the most recent follow-up visit. Bronchopulmonary dysplasia (BPD) was defined as oxygen depen-

dence at 36 weeks post conceptional age. Intraventricular hemorrhage (IVH) was determined from ultrasound examination and graded according to Papile's classcification[7]. Sepsis referred to positive organism from blood culture. Clinical infection defined as symptoms and signs of infection with a significant increasing C-reactive protein but negative blood culture. Highest grade in school was used as an indicator of maternal education.

Outcome measures

The authors considered an abnormal outcome when MDI was less than 70, PDI less than 70, severe neurosensory deficits which included blindness or visual acuity less than 20/200 or hearing loss greater than 40 dB, or severe cerebral palsy (CP) which was defined as spastic hemiplegia or quadriplegia, global hypotonia or chorioathetosis.

Statistics analysis

For univariate analysis, continuous variables were analyzed by unpaired Student's *t* test and dichotomous variables were analyzed by Chi square test. For multivariate analysis, logistic regression procedure was used to analytically estimate the simultaneous effect of a set of predictors for each outcome by using S Plus. Only statistically significant ($p<0.05$) variables from the univariate analysis were entered in the model. In order to assess agreement between the NBRS and outcome variables, the outcomes were coded as abnormal if scores were less than 70 for MDI or PDI or if neurological examination revealed cerebral palsy. A cross tabular method was applied with NBRS risk categories to determine sensitivity, specificity, positive predictive value, and negative predictive value.

RESULTS

Demographic characteristics of 462 infants who met these criteria were analysed. Two hundred and forty-six infants had a birth weight less than 1,000 g and 216 infants had a birth weight between 1,000-1,250 g. Nineteen infants subsequently died; 15 infants of whom had a birth weight less than 1,000 g. One hundred and eighty-five infants (58 with a birth weight less than 1,000 g and 127 with a birth weight between 1,000-1,250 g) were lost to follow-up. Two hundred and fifty-eight infants [173 (75%) infants with a birth weight less than 1,000 g and 85 (40%) infants with a birth weight between 1,000 to 1,250 g] returned to the clinic for developmental follow-up assessment. At the time of data collection, 78 (32%) infants completed this assessment at 36 months of corrected age, and 53 (22%) infants and 74 (30%) infants completed this assessment at 24 and 18 months of corrected age, respectively. Mean age at the latest developmental assessment of all infants was 22 months. Mean birth weight and mean gestational age were 881 g and 28 weeks, respectively. There were 51 per cent females and 80 per cent black. Mean maternal age was 24.6 years; 18.7 per cent of mothers were ≤ 18 years old. Thirty-six per cent had less than 12^{th} grade education and 22 per cent had no prenatal care. Table 1 displays the infants' clinical course and complications.

Forty-eight to 53 per cent of these infants continued to have poor or below average growth as measured by weight, height and head circumference less than 25^{th} percentile for age. Thirty-six infants had a head circumference below 10^{th} percentile; 30 had a birth weight less than 1,000 g. Twenty-two infants (61%) of those who had microcephaly had major neurodevelopment deficits including mental

Table 1. Infant clinical course and complications.

Complications	Number	%
Oxygen dependent at 28 days post-natal age	137	53
Oxygen dependent at 36 weeks post-conceptional age	99	38
Severe intraventricular hemorrhage (grade III-IV)	20	7.8
Periventricular leukomalacia	7	2.7
Clinical infection / sepsis	156	60
Sepsis (positive blood culture)	98	38
Pulmonary air leak syndrome	31	12
Pulmonary interstitial emphysema	21	8.1

Table 2. Neurodevelopmental outcomes.

Parameters	Number	%
MDI < 70	43/246	17
PDI < 70	42/237	18
CP	36/258	14
Diplegia	19	
Quadriplegia	9	
Hemiplegia	6	
Athetosis	2	
Blind	2	
Deaf	3	
Any impairment	71/242	29

MDI = mental developmental index,
PDI = psychomotor developmental index,
CP = cerebral palsy

retardation (n = 13), quadriplegia (n = 5), hemiplegia (n = 3) and athetosis (n = 1).

Table 2 shows neurodevelopmental outcome. Seventeen per cent had MDI less than 70 or in the mental retardation range; 18 per cent had significantly poor motor performance; 14 per cent (36 infants) developed cerebral palsy including 19 diplegia, 9 quadriplegia, 6 hemiplegia, and 2 athetosis. Two infants were blind and 3 were deaf. Any of these impairments occurred in 71 (29%) infants.

Table 3 demonstrates a high association between NBRS and developmental outcomes ($p < 0.001$). The NBRS ≥ 8 was associated with increased risk for having an abnormal MDI, PDI and CP (unadjusted odds ratio = 5.47, 14.92 and 8.03, respectively). The NBRS ≥ 8 had a sensitivity for abnormal outcomes from 25 per cent to 35 per cent and a positive predictive value from 48 per cent to 68 per cent, respectively. Depending upon the outcomes, the specificity and negative predictive values ranged from 94 per cent to 96 per cent and 86 per cent to 89 per cent, respectively (Table 4).

Table 5 shows the result of the multivariate analysis. Birth weight and gestational age were the factors that contributed significantly to the outcomes. Maternal education and amount of prenatal care were significant variables for abnormal MDI and CP (not shown in the table). Variables other than birth weight and gestational age were selected to enter into the models for regression analysis including maternal education, number of prenatal care, maternal cocaine abuse, multiple gestations, gender, APGAR score at 5 minutes ≤ 3, BPD, and NBRS (code 0 if score < 8, code 1 if score ≥ 8). Factors associated with an increased risk for an MDI < 70 included maternal cocaine abuse, multiple gestations, APGAR score at

Table 3. Neurobiologic risk score and developmental outcomes.

NBRS	Prevalence of abnormal neurodevelopment					
	MDI < 70	%	PDI < 70	%	CP	%
≤ 4	23/186	12	19/180	11	18/192	9
5 - 7	9/37	24	8/35	23	6/41	14
≥ 8	11/23	48	15/22	68	12/25	48
P-value	< 0.0001		< 0.0001		< 0.0001	

MDI = mental developmental index, PDI = psychomotor developmental index, CP = cerebral palsy

Table 4. Neurobiologic risk score ≥ 8 and predictive values for major developmental impairments.

NBRS ≥ 8	Major developmental impairment		
	MDI < 70	PDI < 70	CP
Sensitivity	25	36	33
Specificity	94	96	94
Positive Predictive Value	48	68	48
Negative Predictive Value	86	87	90

MDI = mental developmental index, PDI = psychomotor developmental index, CP = cerebral palsy

Table 5. Multivariate analysis : Significant predictors for abnormal outcomes.

Factors	Adjusted Odds Ratio	95% Confidence Interval
MDI < 70		
Cocaine abuse	3.71	1.27-10.78
Multiple gestations	3.74	1.59-8.80
APGAR at 5 min ≤ 3	6.81	1.58-29.34
BPD	2.73	1.27-5.88
NBRS ≥ 8	3.65	1.34-9.94
PDI < 70		
Multiple gestations	3.20	1.29-7.91
APGAR at 5 min ≤ 3	5.81	1.39-24.24
BPD	3.38	1.50-7.59
NBRS ≥ 8	9.39	3.20-27.55
CP		
APGAR at 5 min ≤ 3	6.73	1.85-24.50
NBRS ≥ 8	7.12	2.76-18.39

MDI = mental developmental index, PDI = psychomotor developmental index,
NBRS = neurobiologic risk score, CP = cerebral palsy, BPD = bronchopulmonary dysplasia

5 minutes ≤ 3, BPD, and NBRS ≥ 8 with adjusted odds ratio 3.71, 3.74, 6.81, 2.73 and 3.64, respectively. The variables associated with increased risk of having a subnormal PDI were multiple gestations, APGAR score at 5 minutes ≤ 3, BPD, and NBRS ≥ 8 with adjusted odds ratio of 3.20, 5.81, 3.38 and 9.39, respectively and the significant variables for CP were APGAR score at 5 minutes ≤ 3, and NBRS ≥ 8 with adjusted odds ratio of 6.73 and 7.12, respectively. When infants with a birth weight less than 1,000 g were analyzed separately, maternal education was a significant risk variable for MDI < 70 and CP in addition to the above variables.

DISCUSSION

The incidence of major neurodevelopmental impairment in the present study is comparable to the incidence of 13 per cent to 21 per cent reported in other studies[8-13]. Mortality rate of infants in this group has improved over the past decades, whereas, morbidity rate has remained the same or even improved particularly for very premature infants[8, 13]. The discrepancy in the presented follow-up rate between infants with a birth weight < 1,000 g and above (75% *vs* 40%) might indicate either infants of the later group were doing better or parents had less concern since they had significantly lower rates for abnormal outcomes (12% *vs* 20% for MDI <70, 22% *vs* 8% for PDI < 70 and 17% *vs* 7% for CP) and also had significantly fewer complications during the nursery course. The post-natal growth patterns of the presented infants indicated the continued suboptimal growth. Sixty-one per cent of infants who had a head circumference below the 10th percentile showed severe neurodevelopmental impairment; a finding consistent with other studies which showed that poor head growth during the early months of life is a significant predictor for abnormal outcomes[14-17].

In the present study, the authors defined abnormal outcome as MDI or PDI less than 70 (below 2 standard deviation) which indicated severe functional disabilities, whereas other studies defined abnormal outcomes as MDI or PDI < 85 (below 1 standard deviation) which included those with only borderline or mild disabilities; those classifications may lead to inaccuracy of the incidence of abnormal outcomes since many factors have an impact on the adequacy of the test performance at the time of assessment and even normal infants might have scores in this range. With the definition of abnormal outcomes used in the present study, early intervention is clearly indicated. Brazy et al[2] reported in a population of 199 infants with birth weights < 1,500 g that infants with NBRS more than 5 had a significantly increased risk of abnormal outcomes; scores between 5 to 7 had a 68 per cent chance of minor abnormalities at 24 months and a 32 per cent chance of severe or major handicaps. In the present study, infants with a score of ≥ 5 had a 40 per cent chance of major handicaps, whereas, a score of ≥ 8, the chance of major disabilities increased to 48 per cent for MDI < 70 and 68 per cent for PDI < 70, respectively. Using a score of ≥ 8, specificity and negative predictive values were significantly higher from 86 per

cent to 96 per cent, with moderately high for positive predictive values and relatively low for sensitivity. As NBRS was based on neonatal events that are likely to have irreversible brain injury, this scoring system may partially explain the later developmental outcomes as other studies demonstrated the influences of environment, socioeconomic status and ongoing medical conditions such as chronic lung disease on developmental outcomes[18-23]. However, biological risk factors remained one of the important variables that affected for a long period of time as multivariate analysis in the present study indicated NBRS was a significantly independent predictor for abnormal MDI, PDI and CP during three years of follow-up.

Logistic regression demonstrated that APGAR at 5 minutes of less than 4, multiple gestations, maternal cocaine abuse, and BPD were independent risk factors for poor developmental outcomes; findings in support of the influence of prenatal and postnatal events. Antenatal cocaine exposure has been reported to be associated with abnormal neurobehavioral response during the newborn period and also with an increased risk of cerebral ischemic lesions [24,25]. Not only may cocaine have direct effects, but also its abuse is associated with socio-environmental risks that may influence the child's outcome. Multiple gestations is a well known factor for increasing risks for perinatal-neonatal complications [26] and for abnormal developmental outcomes[27-29]. BPD is also one of the well known risk factors [18-21] as it increased the incidence of lower respiratory tract infection, rehospitalization and delayed development. When infants with a birth weight < 1,000 g were analyzed separately, maternal education was an additional risk factor associated with abnormal MDI or PDI. Race has been shown to influence the developmental outcomes[22], however, in the present study 80 per cent of the population were black; this might explain why there was no difference in outcomes.

SUMMARY

The present findings demonstrate that extremely low birth weight infants are at a high risk for abnormal physical and developmental outcomes; these infants continue to have subpotimal growth and approximately one fourth of infants had major neurodevelopmental impairments. NBRS has a significant correlation with developmental outcomes in these infants through 36 months' corrected age. The relative low sensitivity of NRBS in this population indicates that a high biologic risk will not necessarily predict abnormal outcomes and also indicates that other factors such as prenatal events, post natal environment or socioeconomic status need to be considered for predicting long-term outcomes. However, with high specificity and negative predictive value, NBRS could be helpful for determining the frequency of follow-up visits and early enrollment in an intervention program.

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Neurobiologic risk score ต่อการทำนายผลทางด้านพัฒนาการในระยะยาวของทารกเกิดก่อนกำหนด ที่มีน้ำหนักแรกเกิดน้อยกว่า 1,250 กรัม

ประชา นันท์นฤมิต, พ.บ., Henrietta S. Bada, M.D.**, Sheldon B. Korones, M.D.**, Wenjian Yang, Ph.D.****

วัตถุประสงค์ : เพื่อศึกษาความสัมพันธ์ระหว่าง neurobiologic risk score (NBRS) และพัฒนาการในระยะยาวของทารกเกิดก่อนกำหนดที่มีน้ำหนักตัวน้อยกว่า 1,250 กรัม

วิธีการวิจัย : Observation cohort ในทารก 258 รายที่รอดชีวิต และกลับมาติดตามอย่างต่อเนื่องจนถึงอายุเฉลี่ย 22 เดือน และศึกษาปัจจัยที่มีผลต่อพัฒนาการในระยะยาว โดยอาศัย univariate และmultivariate analysis

ผลการศึกษา : ร้อยละ 48–53 ของทารกเหล่านี้มีการเจริญเติบโตวัดโดยน้ำหนักและส่วนสูงต่ำกว่าเปอร์เซ็นต์ไทล์ที่ 25 ร้อยละ 17 และ 18 มีความบกพร่องทางสติปัญญา (mental developmental index, MDI) และความสามารถในการใช้กล้ามเนื้อ (pschomotor developmental index, PDI) ต่ำกว่า 70 ซึ่งวัดโดย Bayley Scales for Infant Development และร้อยละ 14 มีภาวะสมองพิการ (cerebral palsy) NBRS มีความสัมพันธ์อย่างมีนัยสำคัญ ($p < 0.001$) กับพัฒนาการในระยะยาวโดย NBRS ที่มีค่า ≥ 8 จะมีโอกาสร้อยละ 48 ที่มี MDI < 70 และร้อยละ 68 ที่มี PDI < 70 โดยใช้ค่า cut off ที่ ≥ 8 พบว่าความจำเพาะ (specificity) และ negative predictive value ต่อความผิดปกติในด้านพัฒนาการเท่ากับร้อยละ 86 และ 96 ตามลำดับ โดย Logistic regression พบว่าน้ำหนักเมื่อแรกเกิดและอายุครรภ์เป็นปัจจัยที่สำคัญที่สุดต่อการทำนายผลทางด้านพัฒนาการ

สรุป : ทารกเกิดก่อนกำหนดในการศึกษานี้ มีความเสี่ยงสูงต่อความผิดปกติด้านพัฒนาการในระยะยาว NBRS มีความสัมพันธ์กับผลพัฒนาการ โดยมีความจำเพาะ (specificity) และ negative predictive value สูงมาก ดังนั้นจึงอาจนำมาใช้ประโยชน์ในการคัดแยกกลุ่มเด็ก ซึ่งต้องการการช่วยเหลือในระยะแรกเริ่ม (early intervention) เป็นพิเศษ

คำสำคัญ : ผลทางด้านพัฒนาการ, ทารกเกิดก่อนกำหนด, neurobiologic risk score

ประชา นันท์นฤมิต, Henrietta S. Bada, Sheldon B. Korones Wenjian Yang
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* ภาควิชากุมารเวชศาสตร์, คณะแพทย์ศาสตร์ โรงพยาบาลรามาธิบดี, มหาวิทยาลัยมหิดล, กรุงเทพ ฯ 10400
** Department of Pediatrics and Obstetrics and Gynecology, The University of Tennessee, Memphis, Tennessee, USA.
*** Department of Mathematical Science, The University of Memphis, Tennessee, USA.