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Growth in the Neonatal Intensive Care Unit Influences Neurodevelopmental and Growth Outcomes of Extremely Low Birth Weight Infants

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ABSTRACT

OBJECTIVES. The objectives of this study were to assess whether (1) in-hospital growth velocity is predictive of neurodevelopmental and growth outcomes at 18 to 22 months' corrected age among extremely low birth weight (ELBW) infants and (2) in-hospital growth velocity contributes to these outcomes after controlling for confounding demographic and clinical variables.

METHODS. Infants 501 to 1000 g birth weight from a multicenter cohort study were divided into quartiles of in-hospital growth velocity rates. Variables considered for the logistic-regression models included gender, race, gestational age, small for gestational age, mother's education, severe intraventricular hemorrhage, periventricular leukomalacia, age at regaining birth weight, necrotizing enterocolitis, late-onset infection, bronchopulmonary dysplasia, postnatal steroid therapy for pulmonary disease, and center.

RESULTS. Of the 600 discharged infants, 495 (83%) were evaluated at 18 to 22 months' corrected age. As the rate of weight gain increased between quartile 1 and quartile 4, from 12.0 to 21.2 g/kg per day, the incidence of cerebral palsy, Bayley II Mental Developmental Index (MDI) <70 and Psychomotor Developmental Index (PDI) <70, abnormal neurologic examination, neurodevelopmental impairment, and need for rehospitalization fell significantly. Similar findings were observed as the rate of head circumference growth increased. The in-hospital rate of growth was associated with the likelihood of anthropometric measurements at 18 months' corrected age below the 10th percentile values of the Centers for Disease Control and Prevention 2000 growth curve. Logistic-regression analyses, controlling for potential demographic or clinical cofounders, and adjusted for center, identified a significant relationship between growth velocity and the likelihood of cerebral palsy, MDI and PDI scores of <70, and neurodevelopmental impairment.

CONCLUSIONS. These analyses suggest that growth velocity during an ELBW infant's NICU hospitalization exerts a significant, and possibly independent, effect on neurodevelopmental and growth outcomes at 18 to 22 months' corrected age.

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Key Words
extremely low birth weight infant, growth, neurodevelopmental outcome

Abbreviations
ELBW— extremely low birth weight
MDI—Mental Developmental Index
PDI—Psychomotor Developmental Index
PMA—postmenstrual age
CP— cerebral palsy
NDI—neurodevelopmental impairment
SGA—small for gestational age
NEC—necrotizing enterocolitis
IVH—intraventricular hemorrhage
PVL—periventricular leukomalacia
BPD— bronchopulmonary dysplasia
OR— odds ratio
CI— confidence interval

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POSTNATAL GROWTH FAILURE is the norm for extremely low birth weight (ELBW) infants, especially the sickest infants.[1–4] The NICHD Growth Observational Study[1] demonstrated that, although the rate of weight gain was similar to the reported intrauterine rate of weight gain (~15 g/kg per day), once birth weight was regained, most of the infants between 24 to 29 weeks' gestation did not achieve the median birth weight of the reference fetus of the same postmenstrual age (PMA) at hospital discharge. In fact, at discharge from the NICU or at 36 weeks' PMA, most were less than the comparable 10th percentile birth weight for completed weeks of gestation according to the reference intrauterine growth data reported by Alexander et al.[5] Although nonnutritional factors contribute to the development of growth failure, delays in regaining birth weight and low nutrient intakes also play a major role. Compared with fetal nutrient intakes, the early parenteral and enteral nutritional support received by ELBW infants results in substantial protein and energy deficits that persist for weeks and can be directly related to subsequent postnatal growth restriction.[3,4]

Numerous studies have demonstrated that inadequate early nutrition exerts an adverse influence on long-term developmental outcome.[6] Malnutrition at a vulnerable period of brain development has been shown to result in a decreased number of brain cells as well as deficits in behavior, learning, and memory.[7–9] Based on data derived from nutritional studies conducted in rural Guatemala by the Institute of Nutrition of Central America and Panama (INCAP) from 1969 to 1977 and the long-term follow-up studies on statural growth and intellectual and social achievement conducted in 1988–1989, malnutrition is no longer only considered to result in cognitive deficiencies through brain damage.[10] It most likely alters neurodevelopment by interfering with overall health as well as the child's energy level, rate of motor development, and rate of growth. Extrapolating these concepts to hospitalized ELBW infants suggests that although inadequate nutrition may directly result in brain injury, it may also interfere with overall health by reducing immune competence, resistance to infection, and the energy and nutrients available to support recovery from acute and chronic lung disease and to support an adequate rate of growth and development, let alone catch-up growth, during the hospitalization.

An objective of the Growth Observational Study[1] was to use prospectively collected NICU growth, morbidity, and long-term follow-up data from a large heterogeneous population of ELBW infants to examine the impact of in-hospital growth velocity on outcomes at 18 to 22 months' corrected age. The study's primary hypothesis is that the growth status of ELBW infants at NICU discharge, as reflected by growth velocity (grams per kilogram per day for weight gain or centimeters per week for head circumference growth), is associated with neurodevelopmental outcome, growth percentile, and the incidence of rehospitalization at 18 to 22 months' corrected age.

MATERIALS AND METHODS

The study cohort for this report is a subset of the NICHD Neonatal Research Network Growth Observational Study population.[1] Six hundred (86%) of the 695 infants 501 to 1000 g birth weight who participated in that study survived and were discharged from network NICUs. The families of those infants were invited to participate in network ELBW follow-up programs for a comprehensive assessment at 18 to 22 months' corrected age. Although 495 (83%) of the eligible infants were evaluated, sufficient growth data were only available to calculate growth velocities on 490 infants; early back transfer accounted for the insufficient growth data. In addition, length and head circumference growth data were not available for 1 infant from whom weight gain data were available. The Growth Observational Study was a prospective, cohort study that collected anthropometric data on 1660 infants 501 to 1500 g birth weight.[1] Infants were admitted at ≤24 hours of age to 1 of the network centers between August 31, 1994, and August 9, 1995, survived at least 168 hours, and were free of major congenital malformations. Body weight was recorded daily for a minimum of 14 days or until birth weight was regained, whichever occurred later, and then weekly. Recumbent length and head circumference were determined weekly. Trained research nurses performed these anthropometric measurements as previously described[1] and abstracted study data, including information about maternal and neonatal demographics, selected morbidities, clinical conditions, and nutritional practices, until discharge, transfer, death, or 120 days after birth, whichever came first, using previously described definitions.[2,11,12]

For this report, growth velocity was calculated for the period between the time that the infant regained birth weight and discharge, transfer, age 120 days, or until a body weight of 2000 g was reached, a time point that is referred to as "status."[1] Infants within each 100-g birth weight interval from 501 to 1000 g were then divided into quartiles of in-hospital growth velocity rates. Thus, by design, a similar number of infants from each birth weight interval were assigned to each growth velocity quartile of the follow-up cohort. The birth weight distribution of the study population is displayed in Table 1.

The follow-up assessment has been described in detail.[13] The assessments were performed by certified examiners and included a standardized neurologic examination, Bayley Scales of Infant Development II-R (Mental Scale, Motor Scale, and Behavior Rating Scale), structured parent interviews about medical and social history and functional performance, and anthropometric measurements. Anthropometric measures were plotted

TABLE 1 **Birth Weight Distribution of Study Population**

Birth Weight, g	Growth Study Cohort	Survival to Discharge of Growth Study Cohort, *n* (%)	Survivors in Follow-up Study Cohort, *n* (%)
501–600	61	39 (64)	34 (87)
601–700	136	115 (85)	92 (80)
701–800	163	137 (84)	116 (85)
801–900	144	134 (93)	107 (80)
901–1000	191	175 (92)	146 (83)
Total	695	600 (86)	495 (83)

according to gender and corrected age (postterm) at the follow-up assessment using the 2000 Centers for Disease Control and Prevention growth curves.[14]

The specific aims of this project are to determine if at 18 to 22 months' corrected age, compared with infants in the lowest growth velocity quartile: (1) ELBW infants in the highest weight gain quartile have a lower incidence of Bayley Mental Developmental Index (MDI) and Psychomotor Developmental Index (PDI) scores <70, cerebral palsy (CP), neurodevelopmental impairment (NDI), rehospitalization, and growth (weight, length, and head circumference) below the 10th percentile; (2) ELBW infants in the highest head circumference growth quartile have a lower incidence of MDI and PDI scores <70, CP, and NDI; and (3) that the association between growth velocity and outcome persist after adjusting for demographic and clinical factors that influence outcome. NDI was defined as the presence of any of the following: CP, Bayley MDI <70, Bayley PDI <70, deaf/hearing loss requiring amplification in both ears, or bilaterally blind.

Statistical Analyses

For the purpose of this report, the growth velocity was treated as a 4-level categorical variable that indicated the quartile into which an infant's growth velocity fell. Neurodevelopmental and growth outcomes and rehospitalization were treated as binary variables. Associations between these variables and growth velocity quartile, maternal and neonatal variables, and in-hospital morbidities were explored. Variables included in these analyses were gender, race, gestational age, small for gestational age (SGA) at birth, mother's education, age at regaining birth weight, proven necrotizing enterocolitis (NEC), severe intraventricular hemorrhage (IVH) grades 3 and 4, periventricular leukomalacia (PVL), late-onset infection, bronchopulmonary dysplasia ([BPD] oxygen therapy at 36 weeks' PMA), and postnatal steroid therapy for pulmonary disease. Statistical significance ($P < .05$) was determined by the Kruskal-Wallis test for continuous variables and by χ^2 (Mantel-Haenszel χ^2 or Pearson χ^2) or Fisher's exact tests for categorical variables, as appropriate. Adjusted relationships were evaluated using logistic-regression models to fit the binary outcomes and to identify associations between growth at status and neurodevelopmental and growth outcomes and incidence of rehospitalizations at 18 to 22 months' corrected age. Covariates included in the models were those variables with $P \leq .10$ from the bivariate tests. All analyses were adjusted for center. The results were expressed as adjusted odds ratios (ORs) and 95% confidence intervals (CIs). Analyses were completed at RTI International (Research Triangle Park, NC) by using SAS software (SAS Institute, Inc, Cary, NC).

RESULTS

The characteristics of the infants in the follow-up cohort by weight gain quartile are displayed in Table 2. The average daily rate of weight gain between regaining birth weight and discharge increased from 12.0 to 21.2 g/kg per day from quartile 1 to quartile 4. The rate of length and head circumference growth within each of these weight gain quartiles both increased from 0.8 cm per week to 1.1 cm per week between quartile 1 and quartile 4. At status, body weight was significantly lower in quartile 1 than in the other quartiles, whereas length and head circumference measurements were similar. Because both the postnatal and postmenstrual ages at status fell significantly between quartile 1 and quartile 4, the differences in growth velocity are understandable. Although the overall percentages of the demographic characteristics and incidences of the selected morbidities are similar to that previously observed at NICHD Neonatal Research Network Centers during that time period,[2,11,12] they specifically reflect the characteristics of the infants included in the Growth Observational Study[1]: 51% were female, 49% non-Hispanic blacks, 33% of their mothers had less than a high school education, 25% had severe IVH, 9% proven NEC, 65% late-onset sepsis (culture-positive plus culture-negative, but treated with antibiotics for ≥5 days), 40% BPD, and 48% were treated with postnatal steroids for pulmonary disease. However, in contrast to our earlier report, SGA in this study cohort was defined as birth weight <10th percentile for gender according to Alexander et al.[5] As the rate of weight gain increased between quartile 1 and quartile 4, the incidence of proven NEC, late-onset infection, BPD, and postnatal steroid therapy for pulmonary disease significantly decreased, suggesting that the slowest growth velocity was experienced by the sickest infants. Interestingly, the mean age at regaining birth weight (defined as regaining birth weight and maintaining it for at least 2 days[1]) was significantly lower in quartile 1 and significantly fewer infants in quartile 1 regained birth weight after 18 days of age (the mean age at which infants in the entire study population regained birth weight). However, because the length of time between the age that birth weight was regained and status was significantly lower in quartile 4, and because 13 (10%) infants in quartile 1 compared with 1 (0.8%) infant in quartile 4 never lost weight, we believe that

TABLE 2 **Characteristics of Follow-up Cohort by Weight Gain Quartile**

Variable[a]	Quartile 1 ($n = 124$)	Quartile 2 ($n = 122$)	Quartile 3 ($n = 123$)	Quartile 4 ($n = 121$)	P[b]
Weight gain, mean (SD), g/kg per d	12.0 (2.1)	15.6 (0.8)	17.8 (0.8)	21.2 (2.0)	—
Length growth, cm/wk	0.82 (0.3)	0.91 (0.2)	1.00 (0.2)	1.11 (0.3)	—
Head circumference growth, cm/wk	0.77 (0.2)	0.90 (0.2)	0.96 (0.1)	1.07 (0.2)	—
Birth weight, g	799 (132)	804 (128)	795 (128)	804 (130)	.92
Weight at status, g[c]	1855 (305)	1974 (206)	1976 (218)	1978 (207)	.0006
Length at status, cm	41.5 (2.4)	41.8 (1.7)	41.6 (1.7)	41.7 (1.7)	.83
Head circumference at status, cm	31.2 (1.9)	31.6 (1.4)	31.6 (1.3)	31.4 (1.3)	.64
Gestational age, wk	26.3 (1.9)	26.3 (1.9)	26.2 (1.8)	26.7 (2.4)	.56
Postmenstrual age at status, wk	38.3 (3.7)	37.4 (2.4)	36.5 (2.0)	36.0 (2.0)	<.0001
Postnatal age at status, d	86.3 (25.1)	80.4 (18.2)	74.7 (17.0)	68.2 (17.0)	<.0001
Age at regaining birth weight, d	15.9 (11.0)	17.3 (9.9)	18.8 (8.5)	19.5 (9.1)	.0031
Regained birth weight >18 days, %	35	40	50	49	<.01
Time from regaining birth weight to status, d	72.0 (21.9)	63.6 (16.5)	56.9 (16.0)	50.9 (14.0)	<.0001
Female, %	48	48	48	60	.097
Race, %					.64
Black	44	48	55	50	
White (and other)	44	42	33	38	
Hispanic	12	10	12	12	
SGA, %	18	16	13	21	.61
Education less than high school, %	32	34	36	32	.87
IVH >3, %	23	32	23	26	1.00
PVL, %	5	6	8	3	.81
NEC, proven, %	20	7	5	4	<.001
Late-onset sepsis, %	83	74	52	55	<.001
BPD, %	56	41	30	31	<.001
Postnatal steroid therapy, %	64	56	43	30	<.001

HC indicates head circumference.

[a] Missing data: length growth, 1 infant quartile 1; head circumference growth, 1 infant quartile 1; for quartiles 1 to 4, respectively: length at status: 3, 0, 1, 0; head circumference at status: 2, 0, 1, 0; mother's education: 5, 11, 5, 7; PVL: 2, 1, 1, 1; BPD: 1, 2, 0,2.

[b] Kruskal-Wallis test for continuous variables; Mantel-Haenszel χ^2 or Pearson χ^2 for categorical variables, as appropriate.

[c] Status refers to the date/time point that an infant was discharged, transferred, was age 120 days, or reached a body weight of 2000 g.

differences in severity of illness and fluid management practices provide a probable explanation for this paradoxic observation.

Selected neurodevelopmental and growth outcomes at the18 to 22 months' corrected age follow-up assessment are shown by weight gain quartile in Table 3. As the rate of weight gain increased between quartile 1 and quartile 4, the incidence of CP, MDI and PDI scores <70, abnormal neurologic examinations, and NDI and the need for rehospitalization fell significantly. The rate of weight gain was significantly related to the likelihood of body weight and length measurements below the 10th percentile at 18 to 22 months' corrected age; however, the likelihood of head circumference measurements below the 10th percentile at the follow-up assessment was not associated with the rate of weight gain.

Table 4 displays the results of logistic-regression analyses, adjusted for center, that were run to further examine the relationship between weight gain quartile and neurodevelopment outcomes; variables known at birth or identified during the NICU hospitalization were controlled for in these models. Significant risk factors associated with an increased likelihood of CP were weight gain quartile (quartile 1 versus quartile 4), severe IVH, PVL, and postnatal steroids for pulmonary disease; SGA decreased the risk of CP. Weight gain quartile (quartile 1 versus quartile 4), black race, and BPD were risk factors significantly associated with an increased likelihood of MDI scores <70; female gender decreased the risk. Only PVL and postnatal steroid therapy for pulmonary disease were significantly associated with an increase in the risk of PDI scores <70. Significant risk factors associated with an increased likelihood of NDI were weight gain quartile (quartile 1 versus quartile 4), PVL, and postnatal steroids for pulmonary disease; female gender decreased the risk. SGA (OR: 2.16; CI: 1.22–3.82; $P < .01$), maternal education less than high school (OR: 2.01; CI: 1.28–3.17; $P < .01$), and PVL (OR: 4.32; CI: 1.36–13.73; $P < .05$) were associated with an increased likelihood of body weight below the 10th percentile at 18 to 22 months' corrected age.

The study cohort was also divided into quartiles based on the rate of head circumference growth. As shown in Table 5, the rate of head circumference growth increased from 0.7 to 1.2 cm per week between quartile 1 and quartile 4, and the head circumference at status was also significantly lower in quartile 1, at 30.9 cm. Note that these values for head circumference growth and head circumference at status differ slightly from those displayed in Table 2, in which the study cohort had been

TABLE 3 **Outcomes at 18 to 22 Months' Corrected Age According to Weight Gain Quartile**

Outcome[a]	Quartile 1 ($n = 124$)	Quartile 2 ($n = 122$)	Quartile 3 ($n = 123$)	Quartile 4 ($n = 121$)	P[b]
Weight gain, mean (SD), g/kg per d	12.0 (2.1)	15.6 (0.8)	17.8 (0.8)	21.2 (2.0)	—
Normal neurologic examination	70	77	76	86	<.01
CP, %	21	13	13	6	<.01
MDI	75.7 (18)	77.7 (18)	79.7 (18)	80.9 (15)	.32
MDI < 70, %	39	37	34	21	<.01
PDI	74.8 (19)	77.5 (19)	81.5 (17)	83.3 (14)	<.01
PDI < 70, %	35	32	18	14	<.001
Blind, %					.21
Unilateral	1	1	0	4	
Bilateral	3	1	0	1	
Hearing impairment, %	5	6	3	2	.36
Hearing aids, %	3	3	2	1	.69
Neurodevelopmental impairment, %	55	49	41	29	<.001
Weight <10th percentile, %	58	61	51	46	.03
Length <10th percentile, %	47	43	29	28	<.001
Head circumference <10th percentile, %	31	18	18	22	.098
Rehospitalization, %	63	60	50	45	<.01

[a] Missing data for quartiles 1 to 4, respectively: CP: 2, 5, 3, 6 infants; neurologic examination: 2, 5, 5, 6; MDI scores: 13, 11, 13, 11; PDI scores: 12, 14, 17, 14; blindness: 3, 4, 3, 7; hearing impairment, hearing aids: 5, 4, 4, 6; NDI: 8, 11, 15, 12; weight <10th %: 5, 6, 5, 8; length < 10th %: 4, 4, 4, 7; head circumference <10th %: 3, 4, 4, 7.

[b] Kruskal-Wallis test for continuous variables; Mantel-Haenszel χ^2 or Fisher's exact test for categorical variables, as appropriate.

TABLE 4 **Logistic-Regression Models Examining the Relationship Between Weight Gain Quartile and Neurodevelopmental Outcomes: OR (95% CI) of Selected Risk Factors**

Risk Factor	CP	MDI <70	PDI <70	NDI
Weight gain quartile (quartiles 1 vs 4)	8.00 (2.07–30.78)[a]	2.25 (1.03–4.93)[b]	1.92 (0.86–4.29)	2.53 (1.27–5.03)[a]
Female gender	0.55 (0.28–1.08)	0.49 (0.30–0.81)[a]	0.62 (0.37–1.05)	0.55 (0.36–0.85)[a]
Black race	—	2.50 (1.33–4.69)[a]	—	1.60 (0.92–2.76)
SGA at birth	0.22 (0.06–0.80)[b]	—	—	—
Regained birth weight >18 d	—	1.69 (0.97–2.93)	—	1.59 (0.97–2.61)
Education less than high school	1.95 (0.99–3.83)	1.66 (0.99–2.80)	—	—
Severe IVH	2.53 (1.20–5.34)[b]	1.24 (0.69–2.23)	1.42 (0.75–2.68)	1.24 (0.71–2.16)
PVL	6.89 (2.22–21.42)[c]	2.67 (0.92–7.72	8.13 (2.64–25.0)[c]	3.22 (1.06–9.79)[b]
BPD	—	2.68 (1.46–4.93)[a]	1.42 (0.77–2.61)	1.57 (0.93–2.66)
Postnatal steroids	2.24 (1.08–4.67)[b]	1.17 (0.67–2.05)	2.99 (1.65–5.42)[c]	1.94 (1.18–3.19)[a]
Late-onset sepsis	1.32 (0.54–3.20)	0.85 (0.47–1.54)	1.68 (0.86–3.28)	0.84 (0.50–1.41)

[a] $P < .01$.

[b] $P < .05$.

[c] $P < .001$.

divided into quartiles based on the rate of weight gain. The values for postnatal and postmenstrual ages at status for the head circumference growth quartiles were similar to the values based on weight quartiles (data not shown). Selected neurodevelopmental outcomes at 18 to 22 months' corrected age by quartiles of head circumference growth are displayed in Table 5. As the rate of head circumference growth increased between quartile 1 and quartile 4, the incidence of CP, MDI and PDI scores <70, abnormal neurologic examinations, and NDI fell significantly. In addition, the likelihood of head circumference measurements below the 10th percentile at 18 to 22 months' corrected age was significantly related with the rate of head circumference growth.

Table 6 displays the results of logistic-regression analyses, adjusted for center, that were run to further examine the relationship between head circumference growth quartile and neurodevelopment outcomes; variables known at birth or identified during the NICU hospitalization were controlled for in these models. Significant risk factors associated with an increased likelihood of CP were head circumference growth quartile (quartile 1 versus quartile 4), PVL, and steroids for pulmonary disease; SGA decreased the risk. Head circumference growth quartile (quartile 1 versus quartile 4), black race, Hispanic race, less than high school education, and BPD were risk factors significantly associated with an increased likelihood for MDI scores <70; female gender decreased the risk. PVL and postnatal steroids for pulmonary disease were risk factors significantly associated with an increased likelihood for PDI scores <70; head circumference growth quartile (quartile 1 versus quartile

TABLE 5 **Outcomes at 18 to 22 Months' Corrected Age According to Head Circumference Growth Quartile**

Outcome[a]	Quartile 1 ($n = 124$)	Quartile 2 ($n = 124$)	Quartile 3 ($n = 123$)	Quartile 4 ($n = 118$)	P[b]
Rate of head circumference growth, mean (SD), cm/wk	0.67 (0.17)	0.87 (0.05)	0.98 (0.06)	1.17 (0.15)	—
Head circumference at status, cm	30.9 (1.9)	31.7 (1.2)	31.6 (1.3)	31.7 (1.5)	.0007
Normal neurologic examination, %	64	74	82	89	<.001
CP, %	22	17	11	3	<.001
MDI	74.6 (18)	76.7 (18)	82.2 (16)	80.9 (16)	<.05
MDI <70, %	44	41	23	22	<.001
PDI	72.0 (19)	79.1 (19)	84.1 (15)	82.4 (14)	<.001
PDI <70, %	43	29	12	17	<.001
Blind, %					
Unilateral	2	0	2	4	.23
Bilateral	2	1	3	0	
Hearing impairment, %	5	6	3	3	.47
Hearing aids, %	4	2	2	1	.42
Neurodevelopmental impairment, %	62	51	33	28	<.001
Head circumference <10th percentile, %	35	18	20	16	<.01

[a] Missing data: head circumference growth, 1 infant; for quartiles 1 to 4, respectively: head circumference at status: 1, 1, 0, 0; CP: 2, 8, 3, 3 infants; neurologic examination: 3, 8, 4, 3; MDI scores: 12, 14, 14, 8; PDI scores: 12, 16, 19, 10; blindness: 3, 7, 3, 4; hearing impairment, hearing aids: 4, 8, 3, 4; NDI: 9, 16, 10, 11; head circumference <10th %: 3, 7, 5, 3.
[b] Kruskal-Wallis test for continuous variables; Mantel-Haenszel χ^2 or Fisher's exact test for categorical variables, as appropriate.

TABLE 6 **Logistic-Regression Models Examining the Relationship Between Head Circumference Growth Quartile and Neurodevelopmental Outcomes: OR and 95% CI of Selected Risk Factors**

Risk Factor	CP	MDI <70	PDI <70	NDI
Head circumference growth quartile (quartiles 1 vs 4)	4.10 (1.24–13.59)[a]	2.33 (1.10–4.95)[a]	1.99 (0.95–4.14)	3.64 (1.85–7.18)[b]
Female gender	0.55 (0.28–1.07)	0.48 (0.29–0.79)[c]	0.60 (0.36–1.01)	0.53 (0.34–0.82)[c]
Black race	—	2.48 (1.31–4.68)[c]	—	1.67 (0.96–2.92)
Hispanic race	—	2.46 (1.01–5.96)[a]	—	1.80 (0.80–4.07)
SGA at birth	0.24 (0.07–0.87)[a]	—	—	—
Regained birth weight >18 days	—	1.62 (0.94–2.77)	—	1.51 (0.93–2.46)
Education less than high school	1.75 (0.90–3.39)	1.75 (1.03–2.96)[a]	—	—
Severe IVH	2.03 (0.99–4.18)	1.22 (0.68–2.21)	1.38 (0.73–2.64)	1.14 (0.65–2.00)
PVL	7.06 (2.27–21.91)[b]	2.15 (0.73–6.37)	5.87 (1.91–18.0)[c]	2.51 (0.80–7.91)
BPD	—	2.54 (1.38–4.68)[c]	1.39 (0.75–2.57)	1.50 (0.88–2.55)
Postnatal steroids	2.07 (1.00–4.30)[a]	1.13 (0.64–1.98)	2.78 (1.53–5.03)[b]	1.95 (1.18–3.21)[c]
Late-onset sepsis	1.51 (0.63–3.62)	0.87 (0.48–1.58)	1.80 (0.92–3.53)	0.83 (0.49–1.39)

[a] $P < .05$.
[b] $P < .001$.
[c] $P < .01$.

4) was of borderline significance ($P = .067$). Significant risk factors associated with an increased likelihood of NDI were head circumference growth quartile (quartile 1 versus quartile 4) and postnatal steroids for pulmonary disease; female gender decreased the risk. Head circumference growth quartile (quartile 1 versus quartile 4; OR: 2.30; CI: 1.13–4.69; $P < .05$) and PVL (OR: 3.16; CI: 1.16–8.60; $P < .05$) were associated with an increased likelihood of head circumference below the 10th percentile at 18 to 22 months' corrected age.

DISCUSSION

The analyses performed for this study demonstrated that the in-hospital growth velocity of ELBW infants was associated with neurodevelopmental and growth outcomes and with the incidence of rehospitalization at 18 to 22 months' corrected age. As the rate of weight gain and head circumference growth increased, the incidence of CP, MDI and PDI scores <70, abnormal neurologic examination, and NDI fell (Tables 3 and 5). Furthermore, the influence of growth velocity remained after controlling for variables known at birth or identified during the infant's NICU hospitalization (Tables 4 and 6). In-hospital weight gain and head circumference growth were significantly related to the likelihood that anthropometric measurements would be below the 10th percentile at 18 to 22 months' corrected age (Tables 3 and 5).

Dusick et al[15] previously reported on growth outcomes at 18 to 22 months' corrected age in a cohort of ELBW infants cared for at NICHD Neonatal Research Network Centers in 1993–1994. Forty-six percent of the infants were below the 10th percentile for weight and 43% were below the 10th percentile for length and head circumference at 18 to 22 months' corrected age. The likelihood of weight, length, and head circumference

below the 10th percentile increased as birth weight fell. Additional factors related to poor growth included SGA, severe IVH/PVL, and abnormal swallow and abnormal neurologic examination at 18 to 22 months' corrected age. The current report demonstrates that, in addition to birth weight, in-hospital growth velocity influenced the likelihood of weight, length, and head circumference measurements below the 10th percentile at 18 to 22 months' corrected age.

As shown in Table 2, the infants who experienced the slowest growth velocity had the highest incidence of morbidities (proven NEC, late-onset infection, BPD, and postnatal steroid therapy for pulmonary disease) that affect the provision and use of nutritional support and growth potential. We previously reported that infants with major morbidities regained birth weight later and gained weight more slowly than infants without morbidities[1] and suggested that poorly nourished infants who were gaining weight slowly might be more prone to late-onset infection and to severe BPD. Others have suggested that the degree of undernutrition that occurs in many ELBW infants contributes to poor neurocognitive outcomes.[16]

The higher incidence of NEC in the infants in quartile 1 compared with the other quartiles (20% versus <7%) may have contributed to the slower rate of weight gain observed in infants in that quartile (Table 2). Others[17,18] have reported slower weight gain during the hospitalization in infants with NEC compared with those without NEC. In addition, growth after discharge seems to be related to the severity of NEC; Walsh[17] reported that approximately one third of the infants with severe NEC had body weights that were >2 standard deviations below the mean at 8 months' corrected age and head circumferences that were >2 standard deviations below the mean at 20 months' corrected age. Also, Hintz[19] recently reported that compared with infants without a history of NEC, infants who had NEC managed surgically were significantly more likely to have body weight, length, and head circumference measurements below the 10th percentile at 18 to 22 months' corrected age; infants who had NEC managed medically had anthropometric measurements that were similar to the infants without a history of NEC. Furthermore, neurodevelopmental impairment has been observed more frequently in infants with severe NEC.[17–21] Because of a lack of significance in the bivariate test results, NEC was not included in either logistic-regression model (Tables 4 and 6) examining the relationship between growth and neurodevelopmental outcome.

Poor nutrition is considered a major contributing factor in the pathogenesis of BPD.[22] The logistic-regression analyses demonstrated that BPD or postnatal steroid therapy for pulmonary disease were significantly associated with CP, MDI scores <70, PDI scores <70, and NDI (Tables 4 and 6). Vohr[13] has previously reported logistic-regression analyses in which both BPD and postnatal steroids for pulmonary disease were significant risk factors associated with the likelihood of neurodevelopmental impairment. Furthermore, postnatal steroid therapy for prevention or treatment of BPD has been shown to reduce the rate of weight gain[23,24] and has been increasingly incriminated as a factor contributing to the development of CP and other neurodevelopmental impairments.[25–29]

Previous investigators[30–32] have also reported an association between the severity of neonatal illness and postnatal head growth and have directly correlated head growth with neurodevelopmental outcome. In addition, infants with culture-positive and culture-negative infections are more likely than uninfected infants to have adverse neurodevelopmental outcomes at 18 to 22 months' corrected age and to have a head circumference <10th percentile at 36 weeks' postmenstrual age and at 18 to 22 months' corrected age.[33] Our findings demonstrating an association between the incidence of poor neurodevelopmental outcomes and head circumference measurements below the 10th percentile at 18 to 22 months' corrected age with the rate of in-hospital head circumference growth are consistent with those reports. Hack et al[34] have previously shown that the influence of subnormal head circumference growth persists and is associated with a greater risk of poor cognitive function at school age. Furthermore, the importance of postnatal body weight gain and head circumference growth were recently demonstrated by Latal-Hajnal and coworkers[35]; they reported that the neurodevelopmental outcomes of preterm infants who were appropriate for gestational age at birth, but <10th percentile at 2 years of age were significantly worse than infants who were SGA at birth but >10th percentile at 2 years.

Conclusions drawn from these analyses are limited by the fact that although the NICU growth, morbidity, and follow-up data were collected prospectively in the Growth Observational Study, nutritional practices were not specified during the NICU hospitalization or postdischarge and vary widely between NICHD Neonatal Research Network Centers. In addition, management decisions relating to such practices as the timing of initiation and speed of advancement of enteral feedings were probably determined by the clinical team's impression of an infant's health; specifically, infants thought to be healthier might have been started on enteral feedings sooner and advanced more rapidly. As shown in Table 2, compared with quartile 1, infants in quartile 4 had lower incidences of proven NEC, late-onset infection, BPD, and postnatal steroid therapy for pulmonary disease, and thus may represent primarily healthier infants. Nonetheless, although infants in quartile 4 had the highest rate of weight gain, they seemed to regain birth weight later. However, as noted previously, the explanation for this apparent paradoxic observation probably relates to

differences in severity of illness and management practices. Specifically, the higher rates of morbidities noted in quartile 1 compared with quartile 4 may have resulted in fluid management practices that led to fluid overload or edema, accounting for the observation that birth weight was never lost or regained earlier.[36] This observation emphasizes the importance of closely monitoring the rate of in-hospital growth once birth weight has been regained. Because weight gain of >18 g/kg per day and head circumference growth of >0.9 cm per week are associated with better neurodevelopmental and growth outcomes, if those rates falter, the infant's diet should be reviewed and steps to ensure adequate nutritional support such as by increasing the dietary protein/energy ratio should be taken, if necessary.

CONCLUSIONS

This project was designed to use prospectively collected NICU growth, morbidity, and long-term follow-up data from a large heterogeneous population of ELBW infants to examine the impact of in-hospital growth velocity on outcomes at 18 to 22 months' corrected age. Bivariate analyses demonstrated that as the rate of weight gain increased, the incidence of CP, MDI and PDI scores <70, abnormal neurologic examination, and NDI and the need for rehospitalization fell significantly. Similar findings were observed as the rate of head circumference growth increased. The rate of weight gain was significantly associated with the likelihood of body weight and length measurements below the 10th percentile at 18 months' corrected age, but not head circumference. The rate of head circumference growth was significantly associated with the likelihood of head circumference measurements below the 10th percentile at 18 months' corrected age. In addition, logistic-regression models, adjusted for center, and controlled for variables present at birth or experienced during the hospitalization demonstrated that growth velocity during an ELBW infant's NICU hospitalization exerts a significant, and possibly independent, effect on neurodevelopmental outcomes of ELBW infants at 18 to 22 months' corrected age.

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