POSTNATAL GROWTH IN VLBW INFANTS: SIGNIFICANT ASSOCIATION WITH NEURODEVELOPMENTAL OUTCOME

BEATRICE LATAL-HAJNAL, MD, KURT VON SIEBENTHAL, MD, HELEN KOVARI, MD, HANS U. BUCHER, MD, AND REMO H. LARGO, MD

Objective To study the significance of growth status at birth and postnatal growth on neurodevelopmental outcome in very low birth weight (VLBW) infants.

Study design Growth and neurodevelopment were examined in 219 VLBW (<1250 g) children, 94 small for gestational age (SGA) (<10th percentile) and 125 appropriate for gestational age (AGA) (>10th percentile). Outcome at age 2 was assessed with the Bayley Scales of Infant Development (Mental Developmental Index [MDI], Psychomotor Developmental Index [PDI]) and a standardized neurologic examination.

Results SGA status was not associated with poor neurodevelopmental outcome. However, after adjustment for covariables including cerebral palsy (CP), SGA children with weight <10th percentile at age 2 had lower mean PDI than SGA children with catch-up growth to weight >10th percentile (mean [SD], 89.9 [17.4] versus 101.8 [14.5]; $P < .001$). AGA children with catch-down growth (weight <10th percentile at age 2) were, independent of CP, more likely to have lower mean MDI (94.9 vs 101.7, $P = .05$) and PDI (81.9 vs 95.1; $P < .001$) than AGA children remaining >10th percentile at age 2. They also more frequently had severe CP (22.9% vs 1.2%; $P = .008$).

Conclusions In VLBW children, the course of postnatal growth rather than the appropriateness of weight for gestational age at birth determines later neurodevelopmental outcome. *(J Pediatr 2003;143:163-70)*

Intrauterine growth restriction (IUGR) in term children, especially if coupled with microcephaly, has been associated with a variety of adverse sequelae such as delayed growth and neurodevelopmental disturbances.[1,2] However, the association between IUGR and neurodevelopmental impairment for very low birth weight (VLBW) infants has been controversial. Recent studies on the long-term outcome of small for gestational age (SGA) VLBW infants have found no difference in cognitive functioning[3-5] or in the rate of cerebral palsy[6] after controlling for perinatal and demographic factors. The role of postnatal growth on outcome has been examined in one recent population-based study where postnatal catch-up growth was a favorable predictor for intellectual functioning in SGA term-born male adolescents.[7] In VLBW children, the effect of postnatal growth on neurodevelopmental outcome has not yet been evaluated.

VLBW infants (<1250 g) have been prospectively evaluated for their neurodevelopmental outcome since 1983 in Zurich at the Growth and Development Center. The aim of this study was first to reinvestigate the association between IUGR and outcome and, second, to examine the impact of postnatal growth patterns on neurodevelopmental outcome in SGA and appropriate for gestational age (AGA) VLBW infants.

See editorial, p 145.

AGA	Appropriate for gestational age	MDI	Mental Developmental Index
ANCOVA	Analysis of covariance	PDI	Psychomotor Developmental Index
CP	Cerebral palsy	SGA	Small for gestational age
IUGR	Intrauterine growth restriction	VLBW	Very low birth weight

From Growth and Development Center, University Children's Hospital Zurich, and the University Hospital Zurich, Switzerland.

Supported by a grant from the Swiss National Science Foundation, No. 3200-064047.00/1.

Submitted for publication Sept 20, 2002; revision received Mar 10, 2003; accepted Apr 22, 2003.

Reprint requests: Beatrice Latal-Hajnal, MD, Growth and Development Center, University Children's Hospital Zurich, Steinwiesstrasse 75, CH-8032 Zurich, Switzerland. E-mail: Bea.Latal@kispi.unizh.ch.

0022-3476/2003/$30.00 + 0

10.1067/S0022-3476(03)00243-9

METHODS

Population

We enrolled 354 live-born infants with a birth weight <1250 g in a prospective study. They were recruited in three cohorts between January 1983 and December 1985 (cohort 1, n = 111), March 1988 and December 1989 (cohort 2, n = 99) and July 1992 and June 1994 (cohort 3, n = 144). All infants born during these periods at the University Maternity Hospital Zurich were included in the study because no parents declined participation. The population was almost completely white; 40% of the children (n = 141) had a birth weight below the 10th percentile for their gestational age (SGA); 60% (n = 213) were appropriate for gestational age (AGA).[8] None of the infants had a birth weight above the 90th percentile; 70% were singletons, and 30% (n = 108) were infants from multiple pregnancies. The study was approved by the local Ethics Committee.

Of the 354 infants initially enrolled, 232 survived. None of the surviving infants had a chromosomal disorder or a severe malformation. Overall (71% vs 62%) and birth weight-specific survival rates did not significantly differ between SGA and AGA infants. Survival rates did not change for SGA children and improved for AGA children (53%, 62%, 69%, $P = .10$, χ^2) over the period for the three cohorts. The proportion of surviving children who were AGA increased with decreasing gestational age so that 81% of all infants born with a gestational age <28 weeks were born within −1 to +1 SD of weight for gestational age compared with only 32% of children with GA ≥28 weeks. Growth restriction was predominantly symmetrical; 95% of all SGA children also had lengths and head circumferences below the 10th percentile with no differences between the three cohorts. Twenty-two percent (n = 52) of all surviving infants were twins, 4% (n = 9) were triplets and 2% (n = 5) were quadruplets. No child died after discharge from the nursery. Of the 232 surviving children (SGA n = 99, AGA n = 133), 219 (94%) (94 SGA, 125 AGA) were examined at age 2. The 153 children in cohort 2 and 3 were also seen at nine months. There were 5 SGA and 8 AGA children lost to follow-up because the parents refused to participate or could not be traced.

Perinatal and Demographic Variables

Gestational age was assessed by the last menstrual period and first trimester ultrasonogram. If both ultrasonogram and information on the last menstrual period were unknown, the gestational age was estimated by the method of Dubowitz et al[9] or Ballard et al.[10] Sepsis was diagnosed when there were clinical signs of systemic infection and if at least one blood culture was positive; bronchopulmonary dysplasia (BPD) was defined as oxygen supplementation at day 28 of life and patent ductus arteriosus (PDA) was diagnosed if indomethacin treatment was given.[11] Intraventricular hemorrhage (IVH) was classified according to Papile et al[12] and parenchymal lesions according to De Vries et al.[13] Parenchymal lesions were assessed in cohorts 2 and 3. Echodensities lasting longer than 14 days were also considered as parenchymal lesions. Necrotizing enterocolitis (NEC) was diagnosed for infants classified as Bell's stage II A or higher,[14] and retinopathy of prematurity (ROP) was graded according to international criteria.[15] Socioeconomic status (SES) was estimated by using a 12-point scale based on paternal occupation and maternal education. Scores ranged from 2 to 12, with 2 being the highest and 12 the lowest socioeconomic level.[16]

Growth

Weight, length, and head circumference were measured according to standard anthropometric procedures.[17] *Z* scores at birth were calculated by relating each measurement of the individual infant to a mean and standard deviation that were derived from Swedish and Swiss birth standards.[8] A birth weight below the 10th percentile was considered SGA, that is equal to a *Z* score below −1.282.[18] Weight, length, and head circumference at nine and 24 months were expressed as *Z* scores with reference to Swiss growth curves.[17] At the age of 2 years, weights were not available for five children, and head circumferences and lengths were not available for six children.

Neurodevelopmental Outcome at Age 2

Mental or motor developmental delay as evaluated with the Bayley Scales of Infant Development (BSID)[19] was defined as an mental development index (MDI) or psychomotor development index (PDI) of <84 (below −1 SD). Mental retardation or severe motor developmental delay was defined as an MDI or PDI of <68 (below −2 SD). In addition to the developmental assessment, a standardized neurologic examination modified after Prechtl and Beintema was performed.[20,21] Cerebral palsy (CP) was defined according to Bax.[22] CP was graded as mild, moderate, or severe (irrespective of the result of the PDI) according to Palisano et al.[23] Children were examined at the Growth and Development Center of the Children's University Hospital Zurich by developmental pediatricians experienced with the administration of the BSID and other developmental tests. Examiners were not involved in the neonatal care of the study subjects. The language used was German, and the examiner translated to Italian for a few children. Age of testing was corrected for prematurity. Developmental testing could be performed in all children, but a neurologic examination was not possible in two children because of refusal to be examined.

Statistics

Data were analyzed with Statistica (Statsoft, Stata Corp, College Station, Tex) software. Because the three cohorts did not differ in regard to demographic, maternal, perinatal, and neonatal variables, data were pooled. The *t* test was used for continuous, approximately normally distributed variables, χ^2 for dichotomous variables (or Fisher exact test for small numbers) and nonparametric tests (Mann-Whitney *U* test) for non-normally distributed or ordinal variables. Pearson correlation between *Z* scores of growth variables and MDI and PDI were calculated.

The association between SGA status and outcome was analyzed using analysis of covariance (ANCOVA) for continuous outcome variables (MDI, PDI) and logistic regression for dichotomous outcome variables (CP, MDI <84, MDI <68, PDI <84, PDI <68). The association between neonatal risk factors and outcome was analyzed by univariate analysis. Those variables significantly ($P < .05$) correlating with poor neurodevelopmental outcome (IVH grade 3 or 4 and PDA) were selected for analysis. Other variables were included into the model based on a priori assumptions (GA, SES, and sex). Because multiple birth children develop differently than singletons,[24,25] comparisons between SGA and AGA children were also adjusted for multiple birth status. The term "cohort" was entered into the analysis to adjust for changes in peri- and neonatal practice and care. It represented the period of each cohort. Covariables included into the final model were SES, sex, gestational age, PDA, IVH grade 3 or 4, multiple birth status, and cohort.

For the analysis of the impact of postnatal growth patterns on neurodevelopmental outcome, factors associated with poor postnatal growth patterns were evaluated. The results were as follows: any form of CP with both poor postnatal growth patterns (SGA [<10th age 2], $P = .12$; AGA [<10th age 2], $P = .01$; moderate or severe CP with AGA [<10th age 2], $P = .003$; IVH grade 3 or 4 with SGA [<10th age 2], $P = .04$; and PDA and BPD with AGA [<10th age 2], $P = .005$ and $P = .18$, respectively). Other pre- and perinatal variables, including SES and maternal age, were not associated with poor postnatal growth patterns.

The association between postnatal growth patterns and outcome was examined using ANCOVA and logistic regression including the same covariables as for the analysis of the impact of SGA status. Logistic regression analysis for MDI <68, PDI <68 and for severe CP could not be performed with all covariables because the numbers became too small. In the ANCOVA, moderate or severe CP was adjusted for. In the logistic regression analysis, adjustment for any type of CP was performed. We could not adjust for moderate or severe CP for the variable PDI <84 because all children with moderate and severe CP had a PDI <84. For the outcome variable MDI <84, moderate or severe CP could be entered as a covariable. The results remained practically unchanged if all forms of CP were used as a covariable. We thus used "any CP" as the covariable in the logistic regression model. Because BPD was associated with poor weight gain in this study, BPD status was included into the regression and the ANCOVA model.

RESULTS

Demographic and Perinatal Variables

Compared with AGA infants (n = 133), SGA infants (n = 99) were born with a higher mean gestational age (30.7 weeks [range, 24.9-36.0] vs 27.8 weeks [range, 24.9-30.4]) and a lower mean birth weight (984.8 g [range, 700-1250] vs 1047.5 g [range, 680-1250]) than AGA infants. Peri- and neonatal variables did not differ between these two groups after correction for gestational age. Socioeconomic status was comparable. Multiple birth infants were equally distributed between SGA and AGA infants (28.3% vs 27.8%). No sex difference was found between SGA and AGA infants.

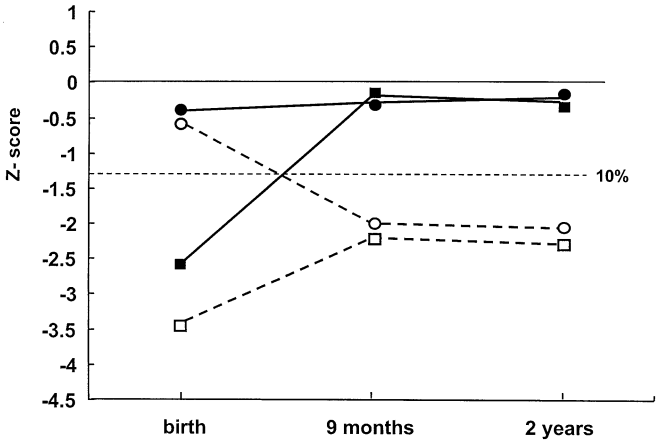

Figure. Mean *Z* scores of weight for different patterns of postnatal growth at birth, nine months and two years. □, SGA: weight <10th percentile at age 2 (n = 52); ■, SGA: weight >10th percentile at age 2 (n = 41): ○, AGA: weight <10th percentile at age 2 (n = 35). ●, AGA: weight >10th percentile at age 2 (n = 86).

Postnatal Growth

Significant differences existed in the extent of catch-up growth for all three growth variables. For weight, SGA and AGA children were further grouped and four distinct subgroups could be identified according to their postnatal growth pattern (Figure). SGA (<10th age 2) represents SGA children with insufficient postnatal weight gain; their weight remained below the 10th percentile at age 2. SGA (>10th age 2) includes SGA children with catch-up growth to >10th percentile at age 2. AGA (<10th age 2) consists of AGA children with catch-down growth resulting in weight below the 10th percentile at age 2 and AGA (>10th age 2) represents AGA children with adequate postnatal growth and weight above the 10th percentile at age 2. Analogous to weight the same categories were created for length and head circumference.

Neurodevelopmental Outcome

Among all VLBW children, 39 (18.2%)* had an MDI <84 and 9 (4.2%) had mental retardation (MDI <68). A PDI <84 was observed in 46 (22%) children, and severe motor developmental delay (PDI <68) in 21 children (10.1%). Moderate or mild CP was diagnosed in 36 (16.4%), and severe CP in 11 (5.0%) children. After adjustment for covariables

*Percentages are calculated for children who were examined. A few children did not have a complete neurodevelopmental assessment; thus the percentages are not exactly the same as if they were calculated for 219 children or for the number given for each subgroup.

Table I. Associations between postnatal growth and neurodevelopmental outcome at age 2 stratified for SGA and AGA children

	Weight		Length		HC	
	SGA N = 94	AGA N = 125	SGA N = 94	AGA N = 125	SGA N = 94	AGA N = 125
Birth						
MDI*	−0.05	0.07	−0.09	−0.01	−0.18	−0.05
PDI*	0.14	−0.03	0.11	0.06	0.04	−0.14
CP†	0.69	0.55	0.01	0.63	0.90	1.58
Age 2						
MDI*	0.11	0.16	0.17	−0.01	−0.03	0.06
PDI*	0.46[c]	0.37[c]	0.42[c]	0.30[c]	0.05	0.17[a]
CP†	−1.86[a]	−3.08[b]	−1.85[a]	−2.90[b]	−0.48	−0.99
Difference birth-age 2						
MDI*	0.13	0.13	0.18	−0.04	0.10	0.09
PDI*	0.29[b]	0.38[c]	0.26[a]	0.21[a]	0.02	0.29[c]
CP†	−2.18[a]	−3.34[c]	−1.20	−2.89[b]	−0.75	−2.08[a]

HC, Head circumference.
Significance is expressed as follows [a]$P \leq .05$, [b]$P \leq .01$, [c]$P \leq .001$.
*Pearson correlation coefficient r is given.
†For cerebral palsy: two tailed t test for independent sample is given.

including Z scores of weight at birth and at age 2, mental, motor, and neurologic outcomes were comparable between SGA and AGA singletons (data not shown).

Postnatal Growth Patterns and Neurodevelopmental Outcome

Z scores of weight, length, and head circumference at birth were not significantly associated with outcome at age 2 for SGA or AGA children (Table I). However, Z scores of weight at age 2 correlated with PDI and with CP in SGA and AGA children. Similar significant associations were found for Z scores of length at age 2. These findings indicated an association between postnatal growth and neurodevelopmental outcome. To verify this association, differences of Z scores between birth and age 2 were correlated with outcome variables. Z score differences of weight and length correlated with PDI and CP.

The association between postnatal growth and neurodevelopmental outcome was analyzed in more detail by using the previously described four subgroups for weight (Table II), length (Table III), and head circumference (Table IV). After adjusting for covariables, including moderate or severe CP, SGA children (<10th age 2) had a lower mean PDI than SGA children (>10th age 2). They also had a higher rate of motor delay; however, after adjustment for CP (any type), the association was not significant anymore (Table V). The result was the same if children with severe CP were excluded from the analysis (data not shown, $P = .10$). SGA children (<10th age 2) had a higher rate of CP (any type) than SGA children (>10th age 2) (Table V).

Children in the AGA (<10th age 2) group had the poorest outcome affecting all areas of development. After adjusting for covariables, including moderate or severe CP, mean MDI was lower for AGA (<10th age 2) children than for AGA (>10th age 2) children (Table II). AGA (<10th age 2) children had the lowest mean PDI of all groups, also after adjustment for moderate or severe CP. Independent of CP, AGA children (<10th age 2) were more likely to exhibit motor delay (PDI <84) than AGA children (>10th age 2) (Table V). AGA children (<10th age 2) were more likely to have CP ($P = .08$). Similar associations between postnatal growth patterns and outcome were noted for length and head circumference (Tables III and IV).

Other factors consistently associated with poor neurodevelopmental outcome are shown in Table V. They included multiple birth status and CP.

DISCUSSION

In this study of VLBW children, postnatal growth pattern rather than SGA status, was found to be significantly associated with adverse neurodevelopmental outcome at age 2. In VLBW children, SGA status at birth was not predictive of later outcome after correcting for perinatal and demographic variables. These findings confirm previous reports of SGA VLBW infants who have been followed until the age of four.[4,5] In our study, SGA status only became a significant predictor of poor outcome, in particular of motor impairment, when it was coupled with insufficient postnatal growth.

Our evaluation revealed that postnatal growth was highly variable among SGA children. Insufficient postnatal catch-up growth has been reported for term and preterm SGA infants and has been shown to persist until adolescence.[1,5] In our study, distinct groups according to postnatal growth pattern could be characterized. There were children

Table II. Postnatal growth pattern and neurodevelopmental outcome at age 2

		Weight				
Weight at birth		**<10th P**	**<10th P**	**>10th P**	**>10th P**	
Weight at age 2		**<10th P**	**>10th P**	**<10th P**	**>10th P**	
Group		**1**	**2**	**3**	**4**	
		N = 52	**N = 41**	**N = 35**	**N = 86**	***P* value***
MDI	Mean (SD)	94.7 (16.6)	98.2 (15.1)	94.9 (22.9)	101.7 (14.7)	3-4[a]
<84	n (%)	12 (23.1)	7 (18.9)	10 (28.6)	9 (10.5)	NS
<68	n (%)	2 (3.9)	0 (0)	6 (17.1)	0 (0)	3-4[c†]
PDI	Mean (SD)	89.9 (17.4)	101.8 (14.5)	81.9 (25.3)	95.1 (15.6)	1-2[c], 1-3[a], 2-3[c], 3-4[c]
<84	n (%)	14 (26.9)	4 (9.8)	16 (45.7)	12 (14.5)	1-2[a], 1-3[a], 2-3[c], 3-4[c]
<68	n (%)	5 (9.8)	1 (2.8)	12 (34.3)	3 (3.6)	1-3[a], 2-3[c], 3-4[c]
CP						
Mild/moderate	n (%)	13 (25.0)	5 (12.5)	6 (17.1)	12 (14.1)	NS
Severe	n (%)	2 (3.8)	1 (2.5)	7 (20.0)	1 (1.2)	1-3[b], 2-3[b], 3-4[b]

*Significance, adjusted for covariables (gestational age, socioeconomic status, sex, cohort, multiple birth status, PDA, BPD, IVH grade III or IV), is expressed as follows [a]$P \leq .05$, [b]$P \leq .01$, [c]$P \leq .001$. The numbers indicate the groups for which level of significance is given. Adjustment performed for continuous outcome variable (MDI, PDI) using ANCOVA, for dichotomous outcome variables logistic regression. Results of ANCOVA include also adjustment for moderate or severe CP.
†*P* value χ^2 without adjustment due to small number of outcome variable.

Table III. Postnatal growth pattern and neurodevelopmental outcome at age 2

		Length				
Length at birth		**<10th P**	**<10th P**	**>10th P**	**>10th P**	
Length at age 2		**<10th P**	**>10th P**	**<10th P**	**>10th P**	
Group		**1**	**2**	**3**	**4**	
		N = 37	**N = 84**	**N = 9**	**N = 83**	***P* value***
MDI	Mean (SD)	90.7 (18.4)	99.0 (15.2)	101.8 (25.4)	100.3 (16.8)	1-2[a], 1-3[a], 1-4[a]
<84	n (%)	11 (29.7)	13 (15.5)	2 (22.2)	12 (14.8)	NS
<68	n (%)	4 (10.8)	0 (0)	1 (11.1)	3 (3.7)	1-2[b†]
PDI	Mean (SD)	86.2 (20.6)	97.9 (15.3)	78.2 (24.0)	93.9 (18.0)	1-2[b], 1-4[b], 2-3[c], 3-4[c]
<84	n (%)	14 (37.8)	10 (11.9)	4 (44.4)	18 (21.7)	1-2[b], 2-3[b]
<68	n (%)	7 (18.9)	3 (3.6)	4 (44.4)	7 (8.4)	1-2[c], 1-3[a], 2-3[c], 3-4[b]
CP						
Mild/moderate	n (%)	8 (22.2)	13 (15.7)	0 (0)	15 (18.1)	NS
Severe	n (%)	5 (13.9)	1 (1.2)	4 (44.4)	1 (1.2)	1-2[a], 2-3[c†], 3-4[c]

*Significance, adjusted for covariables (gestational age, socioeconomic status, sex, cohort, multiple birth status, PDA, BPD, IVH grade III or IV), is expressed as follows [a]$P \leq .05$, [b]$P \leq .01$, [c]$P \leq .001$. The numbers indicate the groups for which level of significance is given. Adjustment performed for continuous outcome variable (MDI, PDI) using ANCOVA, for dichotomous outcome variables logistic regression. Results of ANCOVA include also adjustment for moderate or severe CP.
†*P* value χ^2 without adjustment due to small number of outcome variable.

showing extensive catch-up growth, whereas others remained below the 10th percentile until the age of two years. These different postnatal growth patterns were significantly associated with neurodevelopmental outcome. SGA children who showed substantial catch-up growth with weight above the 10th percentile at age 2 had neurodevelopmental outcomes comparable to AGA children whose weight remained appropriate for age, whereas SGA children who remained below the 10th percentile by age 2 were impaired in their motor development. Few studies have examined the role of postnatal catch-up growth on neurodevelopmental outcome. A population-based study in Sweden described differential outcome in SGA-born 18-year-old males depending on postnatal catch-up growth.[7] Affected outcome was intellectual and psychologic performance. In our study, poor catch-up growth was associated with motor, but less so with mental delay. Because mental abilities can be assessed only in a limited manner at age 2, further follow-up is needed to clarify the role of poor postnatal growth for later intellectual functioning.

Table IV. Postnatal growth pattern and neurodevelopmental outcome at age 2

		Head circumference				
HC at birth		**<10th P**	**<10th P**	**>10th P**	**>10th P**	
HC at age 2		**<10th P**	**>10th P**	**<10th P**	**>10th P**	
Group		**1**	**2**	**3**	**4**	
		N = 47	**N = 91**	**N = 13**	**N = 61**	***P* value***
MDI	Mean (SD)	98.6 (13.6)	99.5 (16.8)	97.0 (16.7)	95.8 (19.6)	NS
<84	n (%)	8 (17.0)	15 (17.1)	2 (15.4)	12 (19.7)	NS
<68	n (%)	1 (2.1)	2 (2.3)	1 (7.7)	4 (6.6)	NS
PDI	Mean (SD)	92.9 (14.4)	97.1 (16.9)	81.8 (16.8)	90.2 (22.5)	1-3[b], 2-3[c], 3-4[a]
<84	n (%)	14 (31.8)	10 (11.4)	6 (46.2)	16 (26.7)	1-2[a], 2-3[b], 2-4[a]
<68	n (%)	3 (7.0)	6 (6.9)	3 (23.1)	9 (15.8)	2-3[a]
CP						
Mild/moderate	n (%)	8 (17.4)	13 (14.4)	3 (23.1)	12 (19.7)	NS
Severe	n (%)	1 (2.2)	3 (3.3)	3 (23.1)	4 (6.9)	2-3[a]

HC, Head circumference.
*Significance, adjusted for covariables (gestational age, socioeconomic status, sex, cohort, multiple birth status, PDA, BPD, IVH grade III or IV), is expressed as follows [a]$P \leq .05$, [b]$P \leq .01$, [c]$P \leq .001$. The numbers indicate the groups for which level of significance is given. Adjustment performed for continuous outcome variable (MDI, PDI) using ANCOVA, for dichotomous outcome variables logistic regression. Results of ANCOVA include also adjustment for moderate or severe CP.

Differences in outcome depending on postnatal catch-up or catch-down growth could not be accounted for by variances in perinatal and neonatal conditions (including BPD) or demographic variables. The proportion of VLBW children who were SGA (40%), that was weight below the 10th percentile at birth, was clearly higher than by definition, namely 10%. This shift towards a higher rate of SGA children was a consequence of the inclusion criteria of the study, a birth weight <1250 g. This selection bias is a known phenomenon of studies on prematurely born infants when definition is given by birth weight rather than by gestational age. However, the large number of SGA children enabled us to stratify them according to postnatal growth and thus to study the influence of postnatal growth patterns on neurodevelopmental outcome.

A variety of conditions may result in SGA status in VLBW infants. In addition to placental insufficiency and IUGR because of prenatal infections, poor maternal weight gain, substance abuse, or multiple birth status, genetic and environmental factors may lead to infants being born SGA.[26] Our results did not change when we controlled for multiple birth status. All mothers had adequate prenatal care and socioeconomic status was not different between the four postnatal growth pattern groups.

The most striking result of this study was postnatal catch-down growth in a group of AGA VLBW children resulting in weight below the 10th percentile at age 2. Their mental and motor functioning was significantly poorer than for AGA children with weight above the 10th percentile at age 2, and even worse than for SGA children with insufficient catch-up growth. Thus, AGA children with catch-down growth had the highest risk for mental retardation, motor delay, and CP among all VLBW children. These findings were mostly independent of the diagnosis of CP. Similar, but less significant, associations were obtained for postnatal catch-down growth of length and head circumference.

How can the association between postnatal growth and developmental outcome be explained? Postnatal weight gain and also stature growth mostly depend on postnatal caloric intake and nutritional quality that, in turn, may be different depending on composition of formula or whether the child received human milk. One recent study reported that VLBW infants fed fortified human milk had a slower growth rate during hospitalization, but an improved health, compared with infants who were fed preterm formula.[27] Absorption rates of zinc and copper were higher in the fortified human milk group. Zinc supplementation of regular term formula has been shown to improve linear growth velocity and motor development in VLBW infants at one year of age.[28] In a randomized study, Lucas et al demonstrated that VLBW infants fed term formula had a disadvantage in overall IQ as well as verbal IQ at age 8 years when compared with infants fed preterm formula.[29] O'Conner et al demonstrated that supplementing premature infant formulas with oils containing long-chain polyunsaturated fatty acids was beneficial for visual acuity and early development in VLBW infants.[30]

Feeding difficulties may also impair postnatal growth. Poor growth has been described in children with CP.[31,32] Postulated mechanisms are immature oral-motor organization as described in preterm infants[33] or impaired oral-motor and neuromotor functioning. The negative effect on later neurodevelopmental outcome may be mediated by insufficient nutritional intake. However, oral-motor dysfunction may also be an early sign of general neuromotor disturbances. Thus, early impairment of oral-motor function may be a confounder of the observed association between postnatal growth and neurodevelopmental outcome.

Table V. Logistic regression models for comparison between different postnatal growth patterns of weight

	MDI <84		PDI <84		CP	
	OR (95% CI)	*P* value	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Group 1-2	1.08 (0.28-4.11)	.91	4.32 (0.70-26.52)	.12	4.34 (1.10-17.12)	.04
Sex (female)	0.98 (0.29-3.34)	.97	5.42 (1.15-25.57)	.04	1.02 (0.30-3.45)	.97
Multiple birth	4.66 (1.34-16.22)	.02	4.17 (1.00-17.38)	.05	3.33 (1.00-11.16)	.05
SES	0.88 (0.69-1.11)	.28	1.23 (0.91-1.65)	.18	0.89 (0.71-1.12)	.34
Cohort	1.28 (0.60-2.73)	.53	0.64 (0.26-1.57)	.33	1.26 (0.60-2.65)	.54
GA	1.00 (0.71-1.43)	.98	0.71 (0.47-1.06)	.10	1.22 (0.86-1.73)	.27
PDA	1.37 (0.17-11.09)	.77	1.63 (0.13-21.11)	.71	1.50 (0.21-10.55)	.68
BPD	0.70 (0.10-4.94)	.72	0.55 (0.05-5.72)	.62	0.20 (0.02-1.66)	.14
IVH 3-4	2.95 (0.27-32.31)	.38	1.21 (0.10-14.14)	.88	2.95 (0.30-28.84)	.36
CP*	1.64 (0.43-6.22)	.47	5.77 (1.18-28.22)	.03		
Group 3-4	1.84 (0.44-7.69)	.40	5.77 (1.15-29.0)	.04	2.60 (0.89-7.63)	.08
Sex (female)	0.89 (0.25-3.21)	.86	2.05 (0.47-9.00)	.35	0.53 (0.19-1.48)	.23
Multiple birth	1.13 (0.29-4.46)	.86	0.37 (0.06-2.32)	.29	1.48 (0.45-4.86)	.52
SES	0.80 (0.59-1.09)	.16	1.11 (0.79-1.56)	.54	0.97 (0.78-1.22)	.82
Cohort	0.65 (0.26-1.63)	.37	0.67 (0.24-1.88)	.44	0.81 (0.40-1.64)	.55
GA	0.62 (0.32-1.20)	.16	0.59 (0.25-1.40)	.23	1.16 (0.71-1.91)	.55
PDA	2.85 (0.37-21.85)	.32	7.68 (0.42-140.56)	.17	2.67 (0.38-18.73)	.33
BPD	1.86 (0.42-8.31)	.42	4.80 (0.79-29.04)	.09	0.76 (0.24-2.42)	.64
IVH 3-4	0.52 (0.07-3.61)	.51	3.68 (0.47-28.96)	.22	3.94 (0.92-16.83)	.07
CP*	7.84 (2.10-29.22)	.003	74.47 (11.15-497.59)	.00002		

Cohort describes the period of which each cohort has been recruited (cohort 1: 1983-85, cohort 2: 1988-89, cohort 3: 1992-94).
Group 1: at birth weight <10th P, at age 2 <10th P, Group 2: at birth weight <10th P, at age 2 >10th P, Group 3: at birth weight >10th P, at age 2 <10th P, Group 4: at birth weight >10th P, at age 2 >10th P.
Logistic regression model with constant variables except for the two poor growth groups in comparison to their corresponding adequate growth group (group 1 versus2, group 3 versus 4).
*CP (any form) as a covariable.

The question whether abnormal neurologic status with poor feeding results in poor growth can only be answered if neurologic status would have been assessed at regular intervals before assessing outcome at age 2. The neurologic examination during the hospital stay of these often ill infants is not reliable enough to use it as a good predictor of outcome. We assessed neurologic status at corrected 9 months for children in cohorts 2 and 3. An abnormal neurologic examination at that time was not associated with poorer weight gain between 9 months and 2 years compared with a normal neurologic examination (data not shown). In addition, independent of moderate or severe CP, children with poor postnatal growth had a lower mean MDI and PDI. Children with catch-down growth also had a higher rate of motor delay, independent of CP. However, this was not true for children with insufficient catch-up growth. This indicates that postnatal growth is an independent factor for adverse outcome, but is probably also partly mediated by CP. We could demonstrate a significant association for poor postnatal growth with neurodevelopmental impairment but not a causal relationship. We think that for clinical practice the poor postnatal growth patterns may be very helpful because they may alert clinicians earlier to closely assess neurodevelopmental status and thus initiate early intervention programs.

Finally, and most importantly, impaired intrauterine growth and development may antecede insufficient postnatal growth. Thus, it may be a marker of impaired central nervous integrity because of adverse intrauterine conditions. Children who were AGA at birth, but became underweight at age 2 may have already been on a catch-down curve before birth. Their postnatal growth course could be the continuation of insufficient intrauterine growth. If pregnancy would have continued until term, those infants may have been born SGA. Insufficient postnatal growth likely reflects impaired intrauterine development. In the future, this hypothesis could be substantiated by repeated intrauterine ultrasonographic measurements demonstrating relative catch-down of growth variables that persist into postnatal life. Ogundipe et al found an association between prenatally detected growth restriction and poor postnatal head growth and motor development in low birth weight (<2500 g) SGA children.[34]

We thank Käthi Etter, Vera Dietz, and Felicitas Steiner for their continuous effort to examine the study patients, and Susanne Ritter for her stimulating discussions.

REFERENCES

1. Strauss RS, Dietz WH. Growth and development of term children born with low birth weight: effects of genetic and environmental factors. J Pediatr 1998;133:67-72.

2. Larroque B, Bertrais S, Czernichow P, Leger J. School difficulties in 20-year-olds who were born small for gestational age at term in a regional cohort study. Pediatrics 2001;108:111-5.

3. McCarton C, Wallace I, Divon M, Vaughan H. Cognitive and neurologic development of the premature small for gestational age infant through age 6: comparison by birth weight and gestational age. Pediatrics 1996;98:1167-78.

4. Sung IK, Vohr B, Oh W. Growth and neurodevelopmental outcome of very low birth weight infants with intrauterine growth retardation: comparison with control subjects matched by birth weight and gestational age. J Pediatr 1993;123:618-24.

5. Gutbrod T, Wolke D, Soehne B, Ohrt B, Riegel K. Effects of gestation and birth weight on the growth and development of very low birth weight small for gestational age infants: a matched group comparison. Arch Dis Child Fetal Neonatal Ed 2000;82:F208-14.

6. Dammann O, Dammann C, Allred E, Veelken N. Fetal growth restriction is not associated with a reduced risk for bilateral spastic cerebral palsy in very-low-birth weight infants. Early Hum Dev 2001;64:79-89.

7. Lundgren EM, Cnattingius S, Jonsson B, Tuvemo T. Intellectual and psychological performance in males born small for gestational age with and without catch-up growth. Pediatr Res 2001;50:91-6.

8. Largo RH, von Siebenthal K, Etter K, Morales C, Bucher H-U, Duc G. Body proportionality in growth-retarded VLBW infants. J Perinat Med 1997;24:17-25.

9. Dubowitz LM, Dubowitz V, Goldberg C. Clinical assessment of gestational age in the newborn infant. J Pediatr 1970;77:1-10.

10. Ballard JL, Novak KK, Driver M. A simplified score for assessment of fetal maturation of newly born infants. J Pediatr 1979;95:769-74.

11. Gersony WM. Patent ductus arteriosus in the neonate. Pediatr Clin North Am 1986;33:545-60.

12. Papile LA, Burstein J, Burstein R, Koffler H. Incidence and evolution of subependymal and intraventricular hemorrhage: a study of infants with birth weights less than 1500 gm. J Pediatr 1978;92:529-34.

13. De Vries LS, Regev R, Pennock JM, Wigglesworth JS, Dubowitz LM. Ultrasound evolution and later outcome of infants with periventricular densities. Early Hum Dev 1988;16:225-33.

14. Bell MJ, Ternberg JL, Feigin RD, Keating JP, Marshall R, Barton L, et al. Neonatal necrotizing enterocolitis. Therapeutic decisions based upon clinical staging. Ann Surg 1978;187:1-7.

15. An international classification of retinopathy of prematurity. Prepared by an international committee. Br J Ophthalmol 1984;68:690-7.

16. Largo RH, Pfister D, Molinari L, Kundu S, Lipp A, Duc G. Significance of prenatal, perinatal, and postnatal factors in the development of AGA preterm infants at five to seven years. Dev Med Child Neurol 1989;31:440-56.

17. Prader A, Largo RH, Molinari L, Issler C. Physical growth of Swiss children from birth to 20 years of age. First Zurich longitudinal study of growth and development. Helv Paediatr Acta Suppl 1989;52:1-125.

18. Tanner JM, Whitehouse RH, Takaishi M. Standards from birth to maturity for height, weight, height velocity, and weight velocity: British children, 1965. I. Arch Dis Child 1966;41:454-71.

19. Bayley N. The Bayley Scales of Infant Development New York (NY): The Psychological Corporation; 1969.

20. Prechtl H, Beintema D. The neurologic examination of the fullterm newborn infant. London: Heinemann Medical Books; 1964.

21. Kuenzle C, Baenziger O, Martin E, Thun-Hohenstein L, Steinlin M, Good M, et al. Prognostic value of early MR imaging in term infants with severe perinatal asphyxia. Neuropediatrics 1994;25:191-200.

22. Bax MC. Terminology and classification of cerebral palsy. Dev Med Child Neurol 1964;6:295-7.

23. Palisano RJ, Hanna SE, Rosenbaum PL, Russell DJ, Walter SD, Wood EP, et al. Validation of a model of gross motor function for children with cerebral palsy. Phys Ther 2000;80:974-85.

24. Petterson B, Nelson KB, Watson L, Stanley F. Twins, triplets, and cerebral palsy in births in Western Australia in the 1980s. BMJ 1993; 307:1239-43.

25. Pharoah PO, Cooke T. Cerebral palsy and multiple births. Arch Dis Child Fetal Neonatal Ed 1996;75:F174-7.

26. La Batide-Alanore A, Tregouet D, Jaquet D, Bouyer J, Tiret L. Familial aggregation of fetal growth restriction in a French cohort of 7822 term births between 1971 and 1985. Am J Epidemiol 2002;156:180-7.

27. Schanler RJ, Shulman RJ, Lau C. Feeding strategies for premature infants: beneficial outcomes of feeding fortified human milk versus preterm formula. Pediatrics 1999;103:1150-7.

28. Friel JK, Andrews WL, Matthew JD, Long DR, Cornel AM, Cox M, et al. Zinc supplementation in very-low-birth-weight infants. J Pediatr Gastroenterol Nutr 1993;17:97-104.

29. Lucas A, Morley R, Cole TJ. Randomised trial of early diet in preterm babies and later intelligence quotient. BMJ 1998;317:1481-7.

30. O'Connor DL, Hall R, Adamkin D, Auestad N, Castillo M, Connor WE, et al. Growth and development in preterm infants fed long-chain polyunsaturated fatty acids: a prospective, randomized controlled trial. Pediatrics 2001;108:359-71.

31. Dahl M, Gebre-Medhin M. Feeding and nutritional problems in children with cerebral palsy and myelomeningocoele. Acta Paediatr 1993;82:816-20.

32. Reilly S, Skuse D, Poblete X. Prevalence of feeding problems and oral motor dysfunction in children with cerebral palsy: a community survey. J Pediatr 1996;129:877-82.

33. Meier P, Anderson GC. Responses of small preterm infants to bottle- and breast-feeding. MCN Am J Matern Child Nurs 1987;12:97-105.

34. Ogundipe EM, Wolfe CD, Seed P, Gamsu HR. Does the antenatal detection of small-for-gestational-age babies influence their two-year outcomes? Am J Perinatol 2000;17:73-81.