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Original Article

Perinatal factors affecting growth and development at age 3 years in extremely low birth weight infants born small for gestational age

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Abstract. Factors affecting growth and development in extremely low birth weight infants (ELBWIs) born small for gestational age (SGA) have not been precisely elucidated. We performed a retrospective analysis of ELBWIs born SGA who were treated in the neonatal intensive care unit of Kawaguchi Municipal Medical Centre, Japan. A total 244 ELBWIs were born from 2003 to 2010, and 31 were born with weight and height below the 10th percentile for their gestational age. Among the 31 ELBWIs born SGA, we excluded 9 who died before they reached 3 yr of age or who had severe developmental retardation. A total of 16 patients (weight, 510–998 g; GA, 28w0d–32w5d) who were followed until age 3 yr were eligible for our study. At age 3 yr, 94% and 88% of ELBWIs were above the −2 standard deviation (SD) for height and weight, respectively. A history of mechanical ventilation was associated with height. The average score of the full developmental quotient (DQ) was 85, and 63% (10/16) of ELBWIs scored more than 85. Lower Apgar score (≤ 7) was a risk factor for lower DQ scores in motor development and full development. Our study revealed that most ELBWIs born SGA were more than −2 SD below the mean for height and body weight.

Key words: Extremely low birth weight infant, small for gestational age, growth, development, Apgar score

Introduction

Recent advances in perinatal care have resulted in significant improvements in the survival of very low birth weight (VLBW) and extremely low birth weight (ELBW) infants (1, 2), however, surviving infants remain at increased risk of less than optimal growth and development. In particular, infants born small for gestational age (SGA) are known to be at increased risk of sequelae compared with appropriate for gestational age (AGA) infants, i.e., neonates born both with VLBW or ELBW and those born SGA are considered at doubled risk for poor growth and developmental outcomes (3–6). Recently, a large-scale retrospective cohort study reported that SGA status in infants born at < 27 week' GA is associated with an increased

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likelihood of mortality, growth failure, and neurodevelopmental impairment at 18–22 months' corrected age (7). However, limited retrospective studies have been performed regarding the long-term outcomes of ELBW infants born SGA (8, 9). The precise clinical course and prognosis of ELBW infants born SGA is unclear, and perinatal risks that might affect postnatal growth and development have not been clarified.

Postnatal growth has been reported to affect neurodevelopmental outcomes in ELBW infants born SGA (10, 11). However, no endocrine parameters seem to be reliable predictors of the linear growth outcome in SGA infants, suggesting the involvement of intrauterine programming or perinatal factors (12). Identifying factors that affect postnatal growth would be beneficial for improving neurodevelopmental outcomes of ELBW infants born SGA.

To identify perinatal factors that affect postnatal growth and neurodevelopmental outcomes in ELBW infants born SGA, we performed a retrospective analysis of ELBW infants born SGA who were treated at a single institute, the neonatal intensive care unit of Kawaguchi Municipal Medical Center in Saitama, Japan. Our analysis was based on strictly standardized treatment and care. In this way, we eliminated biases caused by multicenter research using different treatment and care systems and efficiently identified risk factors for suboptimal growth and development of ELBW infants born SGA.

Materials and Methods

Participants

There were 244 ELBW infants born between 2003 and 2010 at Kawaguchi Municipal Medical Center. We defined SGA as weight and height below the 10th percentile for GA (13). Among 31 ELBW infants who were born SGA, 9 were excluded because they died before reaching age 3 yr or they had severe developmental retardation that suggested underlying congenital diseases. Participants who were suspected of having congenital anomalies or chromosomal anomalies were not included in this study. Six patients were lost to follow-up before the age of 3 yr. Sixteen patients were followed for at least for 3 yr at our institution and were eligible for inclusion in the study (Tables 1a, b). Birth weights and gestational ages of the 9 eligible participants ranged from 510 to 998 g (mean: 838 g) and from 28w0d to 32w5d (mean: 29w4d), respectively. Participants were followed up every 3 mo. The present study complied with the principles of the World Medical Association Declaration of Helsinki regarding ethical conduct of research involving human subjects.

Analyses

We measured body heights and weights at participants' age 3 yr. Participants' development was simultaneously evaluated according to the Kyoto Scale of Psychological Development (14).

We collected data on perinatal factors, including maternal factors (maternal age, weight of placenta) and factors at birth (body weight [BW] and length, gestational age, Apgar score), and postnatal factors (mechanical ventilation, oxygen therapy, breast feeding, hypoglycemia requiring substantial intervention, gastrointestinal problems). We defined substantial therapy for hypoglycemia as continuous high glucose infusion with agents for hypoglycemia, such as glucagon, glucocorticoids, and diazoxide. To analyze nutritional conditions, gastrointestinal problems were included in the analysis, defined as difficulties related to feeding and requiring any medical intervention by a pediatric surgeon.

Correlations between postnatal factors (BW, body length) at birth and at age 3 yr were analyzed using the Pearson's product-moment correlation coefficient. We examined the association between histories of each factor and body size using the Student's *t*-test. All statistical analyses were performed using JMP ver. 10.0 (SAS institute Inc., Cary, NC, USA).

Table 1a Clinical profiles of participants at birth

Case	Birth											
	GA	AS	sex	Ht	BW	HC	MV	O_2	nCPAP	Gast.	HG	Feed
1	29w2d	6/9	M	36	986	26	+	+	+	+	–	–
2	28w2d	6/7	M	33	966	26	+	+	+	+	–	breast
3	29w5d	8/9	M	35	824	24	–	+	–	+	+	breast
4	28w1d	7/8	M	34	870	24	+	+	+	–	–	breast
5	28w4d	8/8	F	34	846	26	+	+	+	–	–	breast
6	28w1d	7/9	M	35	974	26	+	+	+	–	+	breast
7	28w6d	7/8	F	34	922	20	+	–	+	–	–	breast
8	28w5d	7/8	M	35	905	21	+	–	+	–	–	mixed
9	28w1d	8/9	F	33	796	26	+	+	+	–	–	mixed
10	29w5d	5/7	F	33	886	26	+	–	–	–	+	breast
11	28w0d	2/5	M	36	922	26	+	+	+	–	–	mixed
12	28w2d	6/7	M	35	828	24	+	+	+	–	–	breast
13	30w5d	2/5	M	29	620	22	+	+	+	–	–	breast
14	29w2d	2/6	M	35	988	26	–	+	–	–	–	formula
15	32w5d	7/9	F	35	916	27	–	–	–	–	–	breast
16	30w4d	7/9	M	38	972	27	–	+	+	–	+	breast

GA: gestational age, AS: Apgar score, Ht: height, BW: birth weight, HC: head circumference, MV: prolonged mechanical ventilation, O_2: oxygen therapy, nCPAP: nasal continuous positive airway pressure, Gast: gastrointestinal problems, HG: prolonged hypoglycemia, Feed: feeding.

Table 1b Clinical profiles of participants at age 3 yr

Case	Growth at 3 yr				DQ at 3 yr			
	height	SD	weight	SD	Full	Mot.	Cog.	Verval
1	90	–0.94	11.4	–1.49	86	80	89	86
2	90.8	–0.71	13.5	–0.13	83	103	83	81
3	91.1	–0.32	11.7	–0.89	94	106	97	94
4	94.3	0.28	12.6	–0.71	92	103	83	97
5	89.5	–0.79	12.3	–0.51	57	77	58	40
6	89.7	–0.74	11.92	–0.76	95	95	97	90
7	86	–1.8	11.3	–1.15	94	103	97	92
8	89.9	–0.97	11.7	–1.3	86	103	83	89
9	86.6	–1.6	9.8	–2.1	92	103	89	92
10	89.7	–0.73	10.9	–1.4	100	106	106	94
11	95.8	0.71	13.7	0	72	95	77	60
12	87.3	–1.71	10.83	–1.86	46	71	42	39
13	87.6	–1.63	12.2	–0.97	60	74	58	62
14	95.8	1.05	14.7	1.02	89	78	98	86
15	90.3	–0.56	12	–0.71	-	-	-	-
16	88.7	–1.31	10.8	–1.88	83	103	89	78

DQ: developmental quotients, Mot: Motor development, Cog: cognitive development, Verb: verbal development. SD: standard deviation.

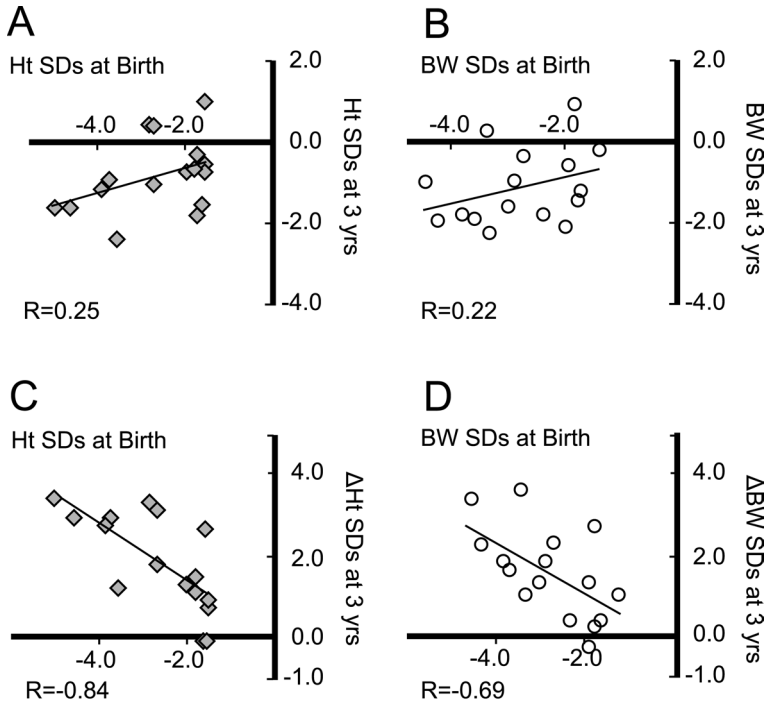

Fig. 1. A: Scatterplot of standard deviations (SDs) for height (Ht) at age 3 yr (Y) against Ht-SDs at birth (X). Pearson correlation coefficient analysis was conducted, and the regression line was plotted; coefficient, R = 0.25. B: Scatterplot of SDs for body weight (BW) at age 3 yr (Y) against SDs at BW-birth (X); coefficient, R = 0.22. C: Scatterplot of SDs for ΔHt-SDs during first 3 yr of life (Y) against Ht-SDs at birth (X). Pearson correlation coefficient analysis was conducted, and the regression line was plotted; coefficient, R = −0.84. D: Scatterplot of SDs in ΔBW-SDs during first 3 yr of life (Y) against BW-SDs at birth (X). Pearson correlation coefficient analysis was conducted, and the regression line was plotted; coefficient, R = −0.69.

Results

Associations of body size at birth and mechanical ventilation with body size at age 3 yr

At age 3 yr, there were 15 (94%) and 14 (88%) participants above the −2 SD for height and BW, respectively. Body size at birth, birth length, and weight were not significantly associated with the same factors at 3 yr of age (Figs. 1A, B). However, the difference in standard deviation score (SDS) between the two time points (i.e., Δ-height SDS and Δ-BW SDS) was associated with body size at birth (Figs. 1C, 1D). This suggests that infants with lower SDs of body size at birth may recover during the first 3 yr of life, leading to no significant association between body size at birth and at age 3 yr.

A history of mechanical ventilation was significantly associated with reduced body height but not BW at age 3 yr. Other perinatal factors, such as Apgar score, history of oxygen therapy, prolonged hypoglycemia, and gastrointestinal problems, did not show such an association (Table 2).

Table 2 Statistical analysis of perinatal factors and body size at participants' age 3 yr

	Apgar Score	History of MV	History of oxygen therapy	Prolonged hypoglycemia	Gastrointestinal problems	Breast feeding
Height	$p = 0.834$	$p = 0.002$*	$p = 0.497$	$p = 0.835$	$p = 0.065$	$p = 0.096$
Weight	$p = 0.364$	$p = 0.108$	$p = 0.786$	$p = 0.352$	$p = 0.075$	$p = 0.306$

Association of lower Apgar score with motor development DQ scores at age 3 yr

The average score of the full developmental quotient (DQ) was 85, and 63% (10/16) of participants scored more than 85 (Table 3). The proportions of participants who scored more than 85 for DQ were 69%, 50%, and 63% for motor, cognitive, and verbal development, respectively. These data suggest that ELBW infants born SGA tended to be delayed in cognitive and verbal development, as reported previously (15).

Apgar score ≤ 7 was a risk factor for lower DQ scores for full scores and for motor development (Fig. 2) but not for cognitive and verbal development (Table 4). Other perinatal factors, such as body size at birth, weight of placenta, mechanical ventilation, oxygen therapy, and gastrointestinal problems, were not significantly associated with the DQ score at age 3 yr.

Table 3 Participant development at age 3 yr evaluated by the Kyoto Scale of Psychological Development

Development	Median score	The propotion of patients whose score > 85
Motor	93	69%
Cognition	85	50%
Verval	85	63%
Full	85	63%

Discussion

Our data revealed that advances in postnatal care and treatment might have improved the growth of ELBW infants. In this study, infants with body heights more than –2 SD at age 3 yr accounted for 94% of participants, which was better than that of reports over 10 yr ago (8). One possible explanation is related to nutrition. In the past 20 yr, the practice of nutrition for preterm infants has increased intake amount and has started nutrition earlier, including parenteral nutrition. Aggressive nutritional support may have helped to improve growth in VLBW infants born SGA.

It is beyond the scope of our study to identify the mechanisms of prolonged mechanical ventilation associated with reduced height at age 3 yr. SGA is a risk factor for bronchopulmonary dysplasia (BPD) (16). During mechanical ventilation, intensive therapy for preventing BPD, such as fluid restriction, diuretics, and corticosteroids, is required, which can negatively impact postnatal growth (17, 18).

In contrast to growth during the first 3 yr of life, improvement in neurodevelopmental outcomes of ELBW infants born SGA was not obvious in comparison with previous reports (9, 15). In our analysis, among perinatal factors, low Apgar score was the only risk factor for developmental delay at the age of 3 yr. This suggests that prenatal factors and not postnatal factors affect neurodevelopment during the first 3 yr of life, and it would be difficult to improve neurodevelopmental outcomes through advances in postnatal management.

Regarding developmental outcomes, we also considered the scoring system used; the data should be interpreted with caution. Although it has been reported that DQ scored using the Kyoto Scale of Psychological Development is equivalent to an IQ score in younger children

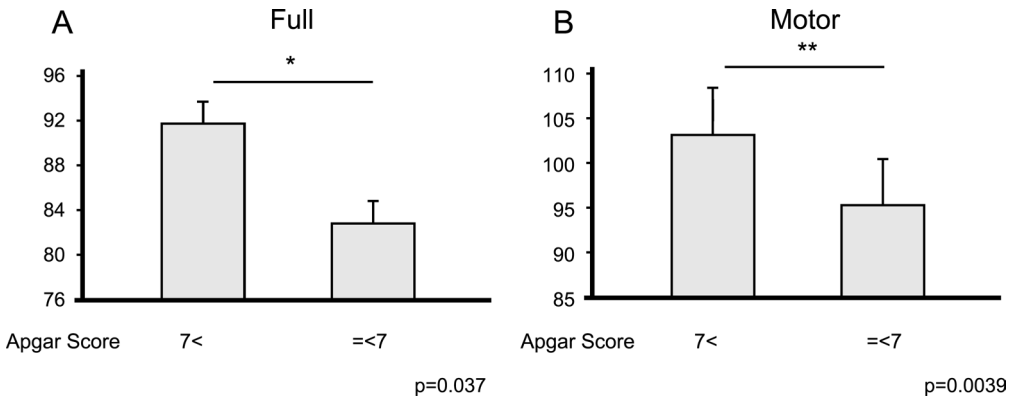

Fig. 2. Lower Apgar score and reduced (A) full and (B) motor development at age 3 yr. Error bars: ± 1 SD. * P < 0.05, ** P < 0.01.

Table 4 Statistical analysis between perinatal factors and body size at participants' age 3 yr

	Apgar Score less than 8	History of MV	Hisotry of oxygen therapy	Prolonged hypoglycemia	Gastrointestinal problems	Breast feeding
Motor	$p = 0.0039$*	$p = 0.766$	$p = 0.253$	$p = 0.263$	$p = 0.968$	$p = 0.601$
Cognition	$p = 0.182$	$p = 0.170$	$p = 0.070$	$p = 0.463$	$p = 0.542$	$p = 0.174$
Verval	$p = 0.075$	$p = 0.064$	$p = 0.546$	$p = 0.932$	$p = 0.681$	$p = 0.112$
Full	$p = 0.037$*	$p = 0.113$	$p = 0.210$	$p = 0.623$	$p = 0.629$	$p = 0.137$

(14), we assume that it may be difficult to directly compare the result of our study with that of previous reports, which were carried out in western countries. Further, the number of cases in our study was limited; to better clarify this issue, a larger number of participants is necessary.

Our study suggested that lower Apgar score might be a risk factor for lower DQ score of motor development at the age of 3 yr. To date, Apgar score is widely accepted as a simple diagnostic test that is a prognostic indicator of asphyxia in neonates. However, it has been reported that the score does not precisely reflect oxygenation in preterm infants, who often have lower scores (19, 20). Because the medical records of our participants lacked data on the pH of umbilical cord blood and other parameters indicating asphyxia at birth, we used the Apgar score instead.

In our study, careful interpretation is necessary regarding the isolated delay of motor development. For identifying mild to moderate cognitive deficits, long-term follow-up is essential (21). Our study data were obtained from 3-yr-old participants and were insufficient to conclude the outcome of cognitive deficits. We speculate that longer follow-up is necessary.

The present study is a longitudinal analysis based on a single medical institute, which would eliminate bias caused by a multicenter study. However, this study has some limitations. In particular, the number of participants is limited compared with a previous study that included 166 participants (8). However, our study provides valuable information for future strategies of care and treatment of ELBW infants born SGA. A large-scale cohort study is necessary to identify factors that affect growth and development at age 3 yr in ELBW infants born SGA.

Conflict of Interest: None of the authors

have any potential conflicts of interest associated with this research.

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