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Reduced growth during early infancy in very low birth weight children with autism spectrum disorder

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1. Introduction

Children born with very low birth weight (VLBW) are at higher risk for developing autism spectrum disorder (ASD) than those born at term [1,2]. Furthermore, approximately one-fourth of VLBW children screen positive for autistic features at 2 years of age, and 2% of VLBW children are diagnosed with ASD as adolescents [1,2]. Despite the high prevalence of ASD and ASD traits in VLBW children, the underlying mechanisms and early biological markers of ASD in this population remain unclear, and it is still unclear whether these children differ from full-term children with ASD.

Full-term children with ASD exhibit an accelerated growth pattern during infancy, particularly in terms of head circumference (HC) [3–6]. This suggests that increased HC in infancy can be related to the brain mechanisms that underlie the manifestation of ASD, and it may serve as an early sign of ASD in this population. Previous studies examining the relationship between early growth patterns and ASD in adults who were born preterm with VLBW have found that faster growth from birth to term was associated with fewer ASD traits in adulthood as assessed by the autism-spectrum quotient, which is a self-report measure [7]. Schrieken etal. [8] examined preterm/low birth weight infants and found that while the non-ASD group showed a disproportionate larger HC in relation to height during the first year of life, this effect was absent in the ASD group. These findings suggested that faster HC growth was associated with favorable social outcomes in preterm children. On the other hand, Moss and Chugani [9] evaluated parent reports and found that rapid HC growth from birth to 24 months in VLBW children was related to increased odds of an autism diagnosis.

Because the findings concerning the relationship between early growth and ASD in VLBW subjects have been inconsistent, an examination of infant growth and its associations with ASD may clarify the mechanisms associated with the increased incidence of ASD in this population. Thus, the present study examined changes in the HC, length, and weight in VLBW children from birth to 18 months of corrected age (CA) to determine whether the growth patterns differed in children with and without ASD and to examine whether there was a critical time period associated with any of these differences.

2. Methods

2.1. Participants

The present study initially included 93 VLBW children who were born before 33 weeks of gestation at Juntendo University between 2004 and 2007 and who were discharged alive; the survival rate was 85.7%. Of the 93 participants, six withdrew from the study prior to the follow-up at 18 months of CA because of relocation. In addition, 26 participants who were missing data for more than three measuring points and 2 participants with severe developmental delays were excluded from the study; therefore, in total, 59 children were assessed in the present study (Fig. 1). None of the participants had a family history of ASD, all participants had provided written informed consent, and all study procedures were approved by the ethics committee at Juntendo University. Of the 59 participants, 9 were diagnosed with ASD (ASD group) during the follow-up visits by two experienced pediatricians based on the criteria from the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text Revision (DSM-4-TR), and 50 were included in the non-ASD group. The average age for diagnosing ASD was 49.1 months (SD 15.7, range 30–74).

Abbreviation: ASD, Autism spectrum disorder; VLBW, Very low birth weight; MDI, Mental Developmental Index; CA, Corrected age; HC, Head circumference.

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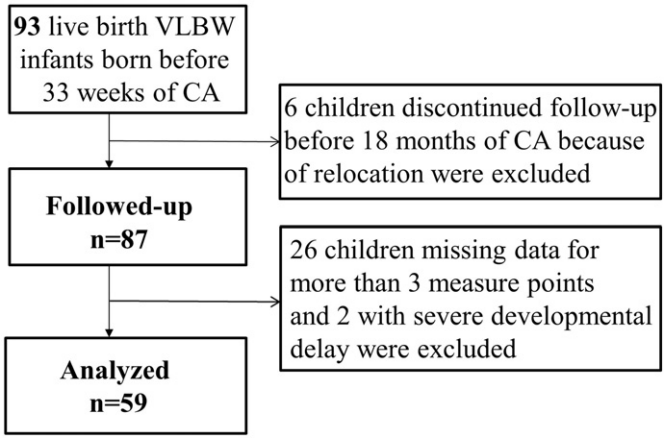

Fig. 1. Flow chart of examined participants of this study. Of the 93 VLBW children, we excluded 6 participants who withdrew from the study prior to the follow-up at 18 months of CA because of relocation, 26 participants who were missing data for more than three measuring points, and 2 participants with severe developmental delays. This resulted in a total of 59 participants for the current study.

2.2. Growth data

The weight, length, and HC measurements of the participants at birth, at term (40 weeks of CA), and at 3, 9, 12, and 18 months of CA were obtained from hospital records. The measurements at birth and term were transformed into Z-scores, according to gestational age and gender based on a Japanese growth chart [10] that provided Z-scores from birth to term-equivalent age. For measurements after 3 months of CA, we utilized a Japanese infant growth chart [11] that provided Z-scores, according to gender and age from 0 months. The CA was used in this analysis.

2.3. Clinical characteristics

Clinical data regarding birth characteristics, neonatal complications, and maternal variables were retrospectively collected from hospital records. The birth characteristics included gestational age at birth, sex, weight, length, and HC at birth, along with the degree to which the child was small for gestational age, defined as a weight at birth and/or length at birth that was two standard deviations (SDs) below the standardized values for the gestational age. The measures of neonatal complications included the Apgar score at 5 min and the incidence of intraventricular hemorrhage (Grades 1–4), respiratory distress syndrome, chronic lung disease (which was defined as a pattern of severe lung injury at 28 days of age in premature infants who were exposed to supplemental oxygen and positive pressure ventilation), necrotizing enterocolitis, and postnatal infections (confirmed by a positive result from blood or cerebrospinal fluid cultures).

We also examined the treatment factors, including the number of days of enteral nutrition required to reach 100 mL/kg/day, the use of postnatal steroids, the use of indomethacin for the treatment of a patent ductus arteriosus, and the use of surfactant for respiratory treatment. Furthermore, we assessed the length of the hospital stays. The maternal characteristics included maternal age, number of previous deliveries, the proportion of single versus multiple pregnancies, pregnancy-induced hypertension, premature rupture of the membranes, antenatal use of steroids, and breastfeeding from birth to discharge. Because some mothers of the children in the ASD group had collagen disease, we also compared the rates of maternal collagen disease between the ASD and non-ASD groups. The developmental statuses of the participants were measured with the Mental Developmental Index (MDI) from the Bayley Scales of Infant Development, second edition [12], at 18 months of CA.

2.4. Statistical analysis

To examine between group differences, Pearson's chi-squared test was used to measure significant differences for categorical variables (i.e. sex, proportion of small for gestational age, neonatal complications such as intraventricular hemorrhage, chronic lung disease, respiratory distress syndrome, necrotizing enterocolitis, infectious disease defined as a culture positive case, steroid treatment after birth, intubation treatment, treatment of PDA by Indomethacin, surgery of PDA, surfactant treatment to RDS, tube feeding after leaving hospital, proportion of maternal characteristics such as multiple pregnancy, primipara, pregnancy induced hypertension, premature rupture of the membranes, administration of steroid before delivery, maternal collagen disease, breast feeding from birth to discharge). Mann-Whitney *U* test was used to compare quantitative continuous variables (i.e. gestational age, Apgar score at 5 min, days of hospital stay, duration until enteral nutrition reach to 100 mL/kg/day, duration of ventilator treatment, MDI at 18 months of CA, age of mother). As for growth data, Z-scores of height, weight, HC at each age point and Z-score changes between each age point were compared between the two groups using Mann-Whitney *U* test. Two-sided p values that were <0.05 were considered to indicate statistical significance.

Furthermore, to clarify which variables were responsible for developing ASD in VLBW children, we performed multivariate logistic regression analysis. The independent variables selected were those that were 1) statistically significant in Mann-Whitney *U* test or Chi-squared test and 2) reported to be a risk factor of ASD in previous studies. Adjusted Odds ratios (ORs) with 95% confidence intervals (CIs) for variables and ASD were calculated to adjust for confounding factors. All data were analyzed with SPSS software version 22.0 (IBM Corporation).

3. Results

3.1. Clinical characteristics

The clinical characteristics of the ASD and non-ASD groups are provided in Table 1. The ASD group had a significantly younger gestational age and a higher proportion of males than the non-ASD group; however, this difference was not significant. The body size at birth, including weight; height and HC, did not differ between the two groups.

In terms of neonatal complications, the ASD group had significantly lower mean Apgar scores at 5 min compared with the non-ASD group. As for treatment factors, there were no significant differences between the two groups. The ASD group also had significantly lower scores on the MDI at 18 months of CA than the non-ASD group.

3.2. Maternal characteristics

The characteristics of the mothers of the participants are shown in Table 1. The mothers of the participants in the ASD group had a significantly higher rate of collagen disease (i.e., systemic lupus erythematosus or Sjögren's syndrome; $\chi^2 = 8.643$, df $= 1$, $p = 0.01$).

3.3. Postnatal growth

Fig. 2 illustrates the average Z-scores for weight, length, and HC for the ASD (continuous line) and the non-ASD (dashed line) groups from birth to 18 months of CA, and Table 2 provides the average change in Z-scores between age points for the two groups. The mean body sizes of the ASD and non-ASD groups did not differ at birth, and although there were no significant differences in terms of the average Z scores for weight, length, and HC between the two groups at any age point, the ASD group tended to be smaller in general. When the Z-score changes were compared at each age point, the ASD group exhibited significantly less growth compared with the non-ASD group in length from