ABSTRACT

Background: The cognitive consequences and risk factors based long-term outcome of very-low-birth-weight (VLBW; < 1,500 g) infants in Korea has not been studied. The aim of this study was to determine the influence of perinatal and neonatal risk factors on the cognitive performance of VLBW children at 3 to 5 years of age.

Methods: We enrolled 88 VLBW infants without cystic periventricular leukomalacia for the assessment of their demographic data, cognitive performance, and development of cerebral palsy (CP) at 3 to 5 years of age. Cognitive performance was assessed using the Korean version of the Wechsler Preschool and Primary Scale of Intelligence IV. Growth data were assessed with measurements of weight, height, and head circumference (HC) at the corrected ages of 6, 12, and 18 months, and 3 to 5 years of age.

Results: In the VLBW group, the full-scale intelligence quotient (FSIQ) was 96.1 ± 15.2 at the mean age of 4.5 years. The incidence rate of CP was 3.4%. Overall, 17% (15/88) of the VLBW children had a below-average FSIQ (< 85). We divided the VLBW children into the abnormal FSIQ group (< 85, n = 15) and the normal FSIQ group (≥ 85, n = 73). VLBW children with intrauterine growth retardation (IUGR) was associated with a below-average FSIQ at the mean age of 4.5 years (< 85, 8/15, 53.3% vs. ≥ 85, 5/73, 6.8%; P < 0.001). After controlling for associated clinical factors, IUGR in the VLBW children was found to be associated with an abnormal FSIQ at the mean age of 4.5 years (P = 0.025). The weight, height, and HC obtained for both groups showed that normal growth was maintained at the mean age of 4.5 years with no significant difference between abnormal and normal FSIQ groups.

Conclusion: Fifteen of 88 (17%) of the VLBW children had a below-average FSIQ (< 85). VLBW with IUGR is associated with poor cognitive outcomes at the mean age of 4.5 years.

Keywords: Very-Low-Birth-Weight Infants; Cognitive Outcome; Intrauterine Growth Retardation
INTRODUCTION

Advances in medical technologies and innovations in the management of very-low-birth-weight (VLBW; < 1.5 kg of birth weight) infants decreased neonatal mortality and morbidity through the late 1990s. However, compared to full-term infants, VLBW infants are prone to a range of long-term complications, such as learning disabilities, attention-deficit hyperactivity disorder, borderline mental retardation, and behavioral disorders. While the incidence of severe cerebral palsy (CP), blindness, and hearing impairment have decreased over time, cognitive impairments have become more prevalent sequelae in VLBW children. Preterm infants born at < 27 weeks of gestation have been reported to show a mean full-scale intelligence quotient (FSIQ) 14.2 points lower than controls at the age of 6.5 years. The greater the immaturity and the lower the birth weight, the greater the likelihood of cognitive disability in the VLBW population. Notably, a recent study reported mild cognitive disability in 30.4% of extremely preterm children, moderate cognitive disability in 18.8%, and severe cognitive disability in 11.1% of preterm children born at < 27 weeks of gestational age (GA) at the age of 6.5 years. Prematurity, perinatal risk factors, and environmental factors are known risk factors for neurodevelopmental impairments, especially with respect to cognitive and executive skills. It was suggested that the influence of extreme prematurity on cognitive disability increases over time after the age of 2.5 years, reflecting a complex relationship between perinatal and environmental factors and cognitive function.

A recent report from the Korean Neonatal Network investigated 2 years’ outcomes of Korean VLBW infants using the Bayley Scales of Infant Developmental Outcomes or the Korean Developmental Screening Test for Infants & Children from various institutions. While the outcome report with a large cohort size provided national initiative for VLBW’s healthcare quality, the low follow-up rate for developmental assessment and heterogeneous data collection from various institutions precluded the authors from assessing the cognitive long-term outcomes adequately for VLBW infants. They recommended a further study of longer follow-up outcomes on the poor cognitive function in VLBW children. Previous studies in Korea have evaluated the neurodevelopmental outcomes of preterm preschoolers using the Korean version of the Wechsler Preschool and Primary Scale of Intelligence IV (WPPSI-IV). However, whether prematurity-related morbidity affects the poor cognitive function remains poorly understood in VLBW children at the age of 3 to 5 years.

Although prematurity birth in itself may adversely affect later development, insight into factors influencing cognitive outcomes is key to improving such outcomes after extremely preterm birth. The aim of this study was to determine the developmental outcomes of VLBW infants at the age of 3 to 5 years as measured by the Korean version of the WPPSI-IV and the factors associated with poor outcomes.

METHODS

This was a prospective cohort study of VLBW infants involving a follow-up program at the Hanyang Inclusive Clinic for Developmental Disorders of the Hanyang University College of Medicine. A total of 140 infants were born and admitted to the level 3 Neonatal Intensive Care Unit at Seoul Hanyang University Hospital between November 1, 2011 and January 1, 2014. The infants received routine follow-up care at the Hanyang Inclusive Clinic for developmental checkups at 3, 6, 12, and 18 months of corrected age, and 3 to 5 years of age. The major
exclusion criteria were genetic syndromes, congenital malformations, chromosomal anomalies and cystic periventricular leukomalacia, because of the increased risk of developing extensive neurological comorbidities with worse outcome even in early life. Of the infants, 124 were discharged, and eighteen of these children were living in other countries or cities. The remaining 106 patients were assessed at the follow-up clinic, at 6, 12, and 18 months of corrected age by a pediatrician who performed a detailed neurological examination and developmental checkups; all had survived to the age of 5 years. The dropout rate was 17% (18/106); the families of 3 infants refused to participate, 9 dropped out from the follow-up, and 6 were withdrawn from the study because of a factor causing the child to be unable to cooperate with testing. The remaining 83% (88/106) of subjects participated in this study at the mean age of 4.5 years (range, 3 years and 8 months to 5 years and 11 months) (Fig. 1).

At 6 and 12 months of corrected age, gross and fine motor skills, posture, tone, reflexes, ankle clonus, and spasticity were assessed by trained neonatologists and a rehabilitationist, focusing on neuromotor function. Children with abnormal muscle tone and neurological examination results were reassessed by a pediatric neurologist. Even if there were no identifiable motor delay and cognitive impairments and at the corrected age of 18 months, neurocognitive assessments including assessment of speech development were recommended for all children at 3 to 5 years of age to assess cognition, language and social functioning. Certified psychologists in the Hanyang Inclusive Clinic for Developmental Disorders assessed cognitive development for VLBW children.

Perinatal data, including maternal age, maternal education, GA, birth weight, sex, Apgar score, type of delivery, antenatal steroid use, and histological chorioamnionitis, were recorded. Intrauterine growth retardation (IUGR) was defined as any fetal growth restriction...
estimated below the 10th percentile of fetal weight that was either observed from serial maternal medical records or from having a birth weight below the 10th percentile based on the growth curve of Olsen et al., together with an abnormal umbilical artery, such as having absent or reversed umbilical artery end-diastolic flow as assessed by fetal Doppler studies. The 3 infants with symmetric IUGR were screened for malformations and chromosomal abnormalities related to chromosomal disorders and clinical findings related to toxoplasmosis, rubella, cytomegalovirus, and herpes simplex virus (TORCH) infections such as hepatosplenomegaly, cardiac lesions, microcephaly, and intracranial calcifications related to IUGR. Clinical abnormalities related to TORCH such as prematurity, hearing impairment, patent ductus arteriosus, thrombocytopenia found during the neonatal period were recorded, as were neonatal sonographic findings and chromosome study results. Placental biopsy findings were gathered for all infants to identify possible causes for placental insufficiency such as placental abruption, extensive infarction, and chorioamnionitis.

We evaluated adverse clinical factors, such as respiratory distress syndrome, patent ductus arteriosus, sepsis, necrotizing enterocolitis (NEC), retinopathy of prematurity (ROP), chronic lung disease (defined as oxygen need at 36 weeks postmenstrual age), and intraventricular hemorrhage (IVH). The diagnosis of NEC was determined as modified Bell’s staging criteria. ROP was classified in accordance with the guidelines of the Committee for Classification of ROP. The use of postnatal steroid was prescribed to treat or prevent bronchopulmonary dysplasia (BPD) after the first week of life. The dexamethasone given for treatment of BPD was considered as the postnatal steroid use. IVH was graded on the basis of cerebral ultrasound findings according to Volpe. Growth parameters (weight, length, and head circumference [HC]) were recorded at corrected age of 6, 12, and 18 months and 3 to 5 years of age. CP was defined in accordance with the definition used by Bax et al. and the classification proposed by the Surveillance of CP in Europe Collaborative Group. The gross motor function of the children with CP was evaluated using the Gross Motor Function Classification System (GMFCS), which is a 5-level classification system (mild CP, GMFCS level 1; moderate CP, GMFCS levels 2 to 3; and severe CP, GMFCS levels 4 to 5). Visual function was assessed by pediatric ophthalmologists and classified in accordance with the modified World Health Organization criteria. Hearing assessment findings were classified as normal, mild hearing loss without audiological intervention, and dependence on hearing aids.

Cognitive development was assessed at the age of 3 to 5 years using the WPPSI-IV. The vocabulary comprehension intelligence quotient (IQ), visual-spatial ability IQ, and working memory IQ were calculated from the subscales. The reference mean (standard deviation [SD]) for the IQs was 100. Mild cognitive disability was defined as an FSIQ of 1 to 2 SDs below the reference mean value of 100 (i.e., 75–84 on the WPPSI-IV); moderate cognitive disability, an FSIQ of 2 to 3 SDs below the mean (i.e., 55–74); and severe cognitive disability, an FSIQ of 3 SDs below the mean (i.e., < 55). No intellectual disability was defined at an IQ of ≥ 85. We divided the VLBW infants into the abnormal IQ group (FSIQ of < 85, n = 15) and the normal IQ group (FSIQ of ≥ 85, n = 73), according to an FSIQ of > 1 SD below the mean. For the analyses of the clinical risk factors influencing cognitive performance, we used an IQ cutoff of < 85 to define intellectual impairment in the study infants.

**Statistical analysis**

All analyses were conducted using SPSS version 22 (IBM Corp., Armonk, NY, USA). Numerical data were analyzed for distribution normality using the Kolmogorov-Smirnov test and are presented as the mean ± SD. Statistical data were calculated using the Mann-Whitney
U-test and Fisher’s exact test for means and frequencies, respectively. The level of statistical significance was set at $P < 0.05$. Logistic regression analyses were performed to analyze the cognitive outcomes, accounting for GA, sex, IUGR, IVH, and maternal education. Differences in WPPSI measures among 3 subscales (vocabulary comprehension IQ, visual-spatial IQ, and working memory IQ) in abnormal IQ group were analyzed in a paired $t$-test and Bonferroni correction of $0.05/3 = 0.016$ for multiple comparison.

**Ethics statement**

The study was approved by the Hanyang University Hospital Institutional Review Board (No. 201501011), and informed consent was obtained from the parents of all enrolled children to participate in the research study.

**RESULTS**

A total of 88 VLBW infants were assessed at a median age of 4.5 years. The mean GA and birth weight were $28.3 \pm 2.8$ weeks and $1,113 \pm 257$ g, respectively. The mean FSIQ was $96.1 \pm 15.2$ (range, $44–132$). Overall, $15/88$ (17%) of the VLBW children had a below-average FSIQ (85). Of the 88 children, 3 (3.4%; 2 moderate and 1 mild case) had CP, and 1 out of 3 children displayed impaired hearing with dependence on hearing aids in the abnormal IQ group. There were no cases of bilateral or unilateral blindness; however, 2 children demonstrated (2.3%) strabismus. The cognitive outcomes according to GA were evaluated using the FSIQ thresholds of $<55$, $<75$, and $<85$ to define cognitive impairment. Cognitive impairment was classified as severe when the IQ was $<55$, moderate at $55$ to $74$, and mild at $75$ to $84$. The number of cases of mild, moderate, and severe cognitive disabilities in the abnormal IQ group was 10, 3, and 2, respectively. The numbers of infants with cognitive impairment and its components distributed by GA are shown in **Table 1**.

The characteristics of the sociodemographic and perinatal data, along with IQ group in the VLBW infants, are shown in **Table 2**. In the abnormal IQ group, the mean vocabulary comprehension IQ was $81.1 \pm 14.5$, the visual-spatial ability IQ was $73.8 \pm 15.4$, the working memory IQ was $84.9 \pm 21.9$, and the FSIQ was $74.5 \pm 13.1$. Notably, the visual-spatial IQ in WPPSI was lower than vocabulary comprehension IQ ($73.8 \pm 15.4$ vs. $81.1 \pm 14.5$; $P = 0.134$) or working memory IQ ($73.8 \pm 15.4$ vs. $84.9 \pm 21.9$; $P = 0.026$) in the abnormal IQ group. However, difference of visual-spatial IQ and working memory IQ remained non-significant after Bonferroni correction for multiple comparisons. In the normal IQ group, the mean vocabulary comprehension IQ was $96.7 \pm 11.9$, the visual-spatial ability IQ was $105.6 \pm 13.6$, the working memory IQ was $102.0 \pm 12.6$, and the FSIQ was $100.6 \pm 11.4$. GA, sex, prenatal steroid and maternal education did not differ between the normal IQ group and the abnormal

### Table 1. Neurodevelopment of very-low-birth-weight children at 4.5 years of age according to GA

| GA, wk | No. Infants | FSIQ $<55$ | FSIQ $<75$ | FSIQ $<85$ | CP | Hearing impaired | Bilateral blindness |
|--------|-------------|------------|------------|------------|----|-----------------|-------------------|
| 24     | 6           | 0 (0)      | 1 (1.1)    | 2 (2.3)    | 0 (0) | 0 (0)           | 0 (0)             |
| 25     | 13          | 0 (0)      | 0 (0)      | 2 (2.3)    | 2 (2.3) | 0 (0)           | 0 (0)             |
| 26     | 5           | 0 (0)      | 1 (1.1)    | 2 (2.3)    | 0 (0) | 0 (0)           | 0 (0)             |
| 27     | 8           | 0 (0)      | 0 (0)      | 0 (0)      | 0 (0) | 0 (0)           | 0 (0)             |
| 28     | 16          | 1 (1.1)    | 1 (1.1)    | 1 (1.1)    | 1 (1.1) | 1 (1.1)         | 0 (0)             |
| ≥ 29   | 40          | 1 (1.1)    | 1 (1.1)    | 8 (9.1)    | 0 (0) | 0 (0)           | 0 (0)             |
| Total  | 88          | 2 (2.3)    | 5 (7.9)    | 15 (17.1)  | 3 (3.4) | 1 (1.1)         | 0 (0)             |

Data are presented as number (%).

GA = gestational age, FSIQ = full scale intelligence quotient, CP = cerebral palsy.
IQ group. There were significant differences in IUGR between the groups. IUGR at birth was associated with a below-average FSIQ at the mean age of 4.5 years (< 85: 8/15 [53.3%] vs. ≥ 85: 5/62 [6.8%]; \(P < 0.001\)). Ten out of the 13 IUGR cases included in the study group demonstrated the asymmetrical type of IUGR.

Table 3 shows the neonatal parameters of both groups and, although no significant differences were found, the abnormal IQ group tended towards a higher incidence of sepsis, NEC, BPD and IVH than the normal IQ group.

The neonatal and perinatal data that might be related to poor cognitive outcomes were analyzed (Table 4). Multiple regression analysis revealed no significant association between GA and cognitive outcomes in the VLBW children. However, after controlling for GA, sex, IVH, and maternal education, only IUGR in the VLBW children affected the cognitive outcomes, with an abnormal vocabulary comprehension IQ (95% confidence interval [CI], 2.543–55.674; \(P = 0.002\)) and FSIQ (95% CI, 1.265–34.557; \(P = 0.025\)) at the mean age of 4.5 years. Table 5 shows the details of individual clinical presentation in study infants with an abnormal FSIQ group.

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measurements showed that the abnormal FSIQ group reached normal weight, height, and HC by 12 months of corrected age. The growth data in 4/15 (26%) infants of the abnormal and 20/73 (27%) infants of the normal FSIQ groups had dropped at the age of 18 months, when the weight in the abnormal FSIQ group was significantly lower than those in the normal FSIQ at the age of 18 months (10.5 ± 1.4 vs. 12.3 ± 2.8; \( P = 0.041 \)). However, all measurements of

### Table 3. Neonatal conditions

| Conditions       | FSIQ < 85 (n = 15) | FSIQ ≥ 85 (n = 73) | \( P \) value |
|------------------|--------------------|--------------------|--------------|
| PDA ligation     | 2 (13.3)           | 12 (16.4)          | 1.000        |
| PDA              | 9 (60)             | 43 (58.9)          | 1.000        |
| Sepsis           | 6 (40)             | 19 (26)            | 0.347        |
| RDS              | 11 (73.3)          | 59 (80.8)          | 0.498        |
| Any NEC          | 5 (33.3)           | 10 (13.7)          | 0.123        |
| Any ROP          | 4 (26.7)           | 7 (9.6)            | 1.000        |
| Any BPD          | 9 (60)             | 31 (42.5)          | 0.261        |
| Ventilator, day  | 14.5 ± 23.9        | 9.4 ± 12.3         | 0.670        |
| Postnatal steroid| 2 (13.3)           | 6 (8.2)            | 0.620        |
| IVH (grade III–IV)| 2 (13.3)        | 5 (6.8)            | 0.177        |
| Hearing impairment| 1 (6.7)           | 0                 | 0.895        |

Data are presented as mean ± standard deviation or number (%).
FSIQ = full scale intelligence quotient, PDA = patent ductus arteriosus, RDS = respiratory distress syndrome, NEC = necrotizing enterocolitis, ROP = retinopathy of prematurity, BPD = bronchopulmonary dysplasia, IVH = Intraventricular hemorrhage.

### Table 4. The multivariate linear regression analysis for risk factors on FSIQ < 85

| Variables            | VCIQ | VSIQ | WMIQ | FSIQ |
|----------------------|------|------|------|------|
|                      | \( \text{Adjusted OR} \) | \( 95\% \text{ CI} \) | \( P \) value | \( \text{Adjusted OR} \) | \( 95\% \text{ CI} \) | \( P \) value | \( \text{Adjusted OR} \) | \( 95\% \text{ CI} \) | \( P \) value |
| GA                   | 1.090 | 0.876–1.357 | 0.439 | 1.123 | 0.892–1.414 | 0.322 | 1.090 | 0.772–1.297 | 0.996 |
| Sex                  | 1.720 | 0.537–5.314 | 0.346 | 0.797 | 0.237–2.681 | 0.714 | 0.349 | 0.081–1.478 | 0.566 |
| IUGR                 | 11.898 | 2.543–55.674 | 0.002 | 3.212 | 0.713–14.460 | 0.129 | 2.263 | 0.403–12.708 | 0.354 |
| IVH (III–IV)         | 3.352 | 0.570–19.721 | 0.181 | 1.773 | 0.289–10.898 | 0.536 | 8.607 | 1.595–46.452 | 0.072 |
| Maternal education   | 1.100 | 0.330–3.667 | 0.876 | 0.814 | 0.217–3.030 | 0.760 | 1.092 | 0.234–5.095 | 0.911 |

OR = odds ratio, CI = confidence interval, GA = gestational age, VCIQ = vocabulary comprehension intelligence quotient, VSIQ = visual spatial intelligence quotient, WMIQ = working memory intelligence quotient, FSIQ = full scale intelligence quotient, IUGR = intrauterine growth retardation, IVH = intraventricular hemorrhage.

*Controlling for GA, sex, IVH, and maternal education.

### Table 5. Details of individual clinical presentations of infants with FSIQ < 85

| Patients | GA, wk | Sex | BW, g | A/S | IUGR | CA | PIH | Sepsis | NEC | BPD | IVH, grade | ROP | CP | Hearing impaired | FSIQ |
|----------|--------|-----|-------|-----|------|----|-----|--------|-----|-----|------------|-----|----|------------------|------|
| 1        | 27-2 M | 660 | 1–3   | +   | +    | –  | –   | +      | +   | +  | 2          | +   | –  | –                | 81   |
| 2        | 30+3 M | 910 | 1–2   | +   | –    | –  | +   | –      | –   | –  | –          | –   | –  | –                | 84   |
| 3        | 30+1 F | 680 | 1–3   | +   | +    | –  | –   | –      | +   | +  | 1          | –   | –  | –                | 73   |
| 4        | 28+5 M | 640 | NA    | +   | –    | –  | –   | –      | –   | –  | –          | –   | –  | –                | 73   |
| 5        | 33+0 M | 1,330 | 2–6 | –    | –    | +  | –   | –      | –   | –  | –          | –   | –  | –                | 84   |
| 6        | 32+1 F | 1,230 | 4–7 | +   | –    | –  | –   | +      | +   | +  | 2          | +   | –  | –                | 80   |
| 7        | 32+4 M | 1,380 | 3–8 | –   | –    | –  | +   | –      | –   | –  | –          | +   | –  | –                | 75   |
| 8        | 32+6 M | 1,420 | 6–9 | –   | –    | –  | –   | –      | –   | –  | –          | –   | –  | –                | 84   |
| 9        | 32+6 F | 1,420 | 6–9 | –   | –    | –  | –   | –      | –   | –  | –          | –   | –  | –                | 84   |
| 10       | 29+0 F | 980 | 1–4   | –   | –    | –  | –   | +      | +   | +  | 1          | –   | –  | –                | 82   |
| 11       | 24+3 F | 620 | 1–2   | –   | –    | –  | +   | –      | –   | –  | –          | –   | –  | –                | 82   |
| 12       | 30+0 M | 980 | 3–5   | –   | –    | –  | –   | –      | –   | –  | –          | –   | –  | –                | 82   |
| 13       | 32+6 F | 1,480 | 7–8 | –   | –    | –  | –   | –      | –   | –  | –          | –   | –  | –                | 80   |
| 14       | 31+6 F | 1,290 | 6–8 | –   | –    | –  | –   | –      | –   | –  | –          | –   | –  | –                | 84   |
| 15       | 32+5 F | 940 | 1–3   | +   | –    | –  | –   | –      | –   | –  | –          | –   | –  | –                | 49   |

GA = gestational age, BW = birth weight, M = male, F = female, NA = not available, A/S = Apgar score, IUGR = intrauterine growth retardation, CA = histologic chorioamnionitis, PIH = pregnancy induced hypertension, NEC = necrotizing enterocolitis, BPD = bronchopulmonary dysplasia, IVH = Intraventricular hemorrhage, ROP = retinopathy of prematurity, CP = cerebral palsy, FSIQ = full scale intelligence quotient.
weight, height, and HC obtained for both groups at the mean age of 4.5 years of cognitive assessment indicated that normal growth was maintained until the mean age of 4.5 years with no significant difference between abnormal and normal FSIQ groups.

**DISCUSSION**

We analyzed data from 88 VLBW infants to investigate the cognitive outcomes and associated risk factors for poor cognitive performance at the mean age of 4.5 years. Seventeen percent (15/88) of the VLBW children had cognitive disability, with an FSIQ of 1 SD below the reference mean value. Of the 88 VLBW children, 73 (83%) had no disability, 10 had mild cognitive disability, and 5 had either moderate or severe cognitive disability at the age of 4.5 years. Except the IUGR, the sociodemographic, perinatal data and growth data did not differ between the normal IQ group and the abnormal IQ group. Our results show a strong association between IUGR and reduced cognitive performance at the mean age of 4.5 years in VLBW infants, after accounting for perinatal and environmental risk factors.

Despite the apparent progress of neonatal clinical practices, VLBW infants born in the prenatal corticosteroid and surfactant era remain at a high risk for cognitive deficits, reduced ability for sustained attention, and poor spatial working memory and school performance with the lack of clear brain injury. Serenius et al. showed that the FSIQ of children born in Sweden at a GA of < 27 weeks from 2004 to 2007 was 14.2 points lower than that of term infants when measured using the WPPSI-IV. They emphasized that the cognitive disability rate is better recognized and more easily detectable in older children from 2.5 to 6.5 years than in those under 2.5 years old, reflecting higher cognitive impairment rates with advancing age. Ballot et al. found that approximately one-third of infants were identified as being at risk for neurodevelopmental delay, however, neither birth weight nor GA predicted the neurodevelopmental outcomes. Twilhaar et al. emphasized that early recognition and identification of risk factors for cognitive outcomes may contribute to long-term outcomes after very preterm birth.

Previous studies have shown an association between IUGR and cognitive disability among children, IUGR, often defined as a disorder of growth and development due to decreased nutrients and oxygen supplied to the fetus, is caused by placental insufficiency during either the prenatal or perinatal period. In even term-born infants, the IUGR accompanied by an abnormal fetal doppler ultrasound and small GA may have a profound impact on adverse

| Table 6. Growth data for very low birth weight infant |
|------------------------------------------------------|
| Variables | 6 mon | 12 mon | 18 mon | 4.5 yr |
| FSIQ < 85  |
| No.       |       |       |       |       |
| Weight, kg| 6.6 ± 1.6 | 9.1 ± 1.5 | 10.5 ± 1.4 | 17.9 ± 3.4 |
| Height, cm| 63.4 ± 5.5 | 74.9 ± 3.5 | 80.4 ± 2.8 | 108.2 ± 4.7 |
| HC, cm    | 40.4 ± 2.9 | 43.8 ± 2.1 | 45.3 ± 2.4 | 51.7 ± 1.5 |
| FSIQ ≥ 85 |
| No.       |       |       |       |       |
| Weight, kg| 7.2 ± 1.2 | 9.3 ± 1.2 | 12.3 ± 2.8 | 18.9 ± 6.8 |
| Height, cm| 63.9 ± 3.9 | 73.2 ± 3.3 | 80.8 ± 3.8 | 110.7 ± 3.9 |
| HC, cm    | 41.4 ± 2.2 | 44.3 ± 4.7 | 46.5 ± 1.6 | 51.5 ± 3.4 |

Data are presented as mean ± standard deviation. FSIQ = full scale intelligence quotient, HC = head circumference. *P < 0.05 compared with weight of FSIQ ≥ 85 group.
cognitive outcome. Previous study reported that 15% of children born at term with IUGR presented an abnormal cognitive performance, with an FSIQ less than 85 at the age of 9 to 10 years. Geva et al. demonstrated that term-born children with IUGR had lower IQs and marked problems including language and neuropsychologic profiles at the age of 9 years. These findings are consistent with those of previous studies showing that higher hyperactivity and conduct problems at the school-going age are associated with IUGR. Meta-analysis and systematic review have already shown the associations between IUGR in children born at term and neurodevelopmental outcomes in school-age children.

A previous study on small-for-GA (SGA) infants born at a GA of < 27 weeks also showed a strong association with adverse cognitive disability on the Bayley Scales of Infant and Toddler Development-Third Edition (BSID-III) compared to the non-SGA group. However, it is important to distinguish between infants who are constitutionally SGA in birth weight and those who have growth restrictions due to pathological conditions, such as congenital, genetic, inflammatory, and infectious diseases. A systematic review of a total of 16 studies has reported that preterm birth with IUGR is associated with significant neonatal morbidity and mortality and poor neurodevelopmental outcomes within 6 months to 3 years compared with appropriate-for-GA (AGA) birth according to the BSID-III and WPPSI-IV. However, these studies on preterm infants with IUGR were limited by their small sample size and have shown conflicting results regarding long-term neurodevelopmental outcomes.

The present study demonstrates the adverse effects on cognitive function of IUGR in VLBW children at the mean age of 4.5 years. IUGR birth in VLBW infants was associated with lower cognitive scores at a mean age of 4.5 years, reflecting the developmental vulnerability with the combined effects of IUGR and extreme prematurity. These findings are consistent with Sung et al. who showed that FSIQ of VLBW infants with IUGR was lower than that of VLBW infants without IUGR. Furthermore, preterm infants with lower GA may be more vulnerable to long-term outcomes with regard to cognitive development than preterm infants with higher GA. Compared with term-born infants with IUGR, preterm infants with IUGR are at higher risk of perinatal and postnatal complications, such as premature birth, IVH, lung disease and sepsis. Previous studies reported that VLBW infants with IUGR carry a significantly higher risk of long-term cognitive sequelae compared with term infants with IUGR, after adjustment for perinatal and neonatal morbidities. The primary mechanisms underlying the association between IUGR and subsequent cognitive outcomes may depend on additional risks to morbidity, such as respiratory distress syndrome, sepsis, and chronic lung disease, but these require further investigation. Another factor implicated in the pathogenesis of both IUGR and cognitive dysfunction in VLBW infants is hypoxia caused by placental insufficiency, which affects the gray matter despite the “brain-sparing” effect. IUGR has consequences on the developing brain associated with long-term impairments in both functional and structural changes, affecting white matter microstructure alterations and gray matter differences. Tolsa et al. described a significant reduction in intracranial volume and cerebral cortical gray matter in preterm newborns with IUGR, compared with AGA preterm newborns.

In summary, our study highlights long-term neurodevelopmental outcomes and the potential influence of IUGR in VLBW infants on their cognitive outcomes at the age of 4.5 years. IUGR at birth is a potential risk factor for lower cognitive performance in VLBW children at the age of 4.5 years. This finding emphasizes the need to investigate long-term cognitive delay related to IUGR in VLBW children for early interventions targeting efficient long-term cognitive performance.
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