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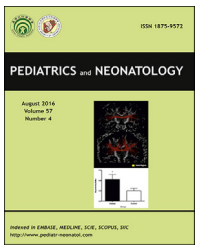

Original Article

Neurodevelopmental outcomes of infants with very low birth weights are associated with the severity of their extra-uterine growth retardation

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Key Words
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Background: For infants with very low birth weights (VLBW), their neurodevelopmental outcomes are thought to be associated with extra-uterine growth retardation (EUGR). In this study, based on a single institute, we analyzed the association between different levels or severity of EUGR of VLBW infants and their neurodevelopmental outcomes later at a corrected age of 24 months.
Methods: This is a hospital-based retrospective cohort study. The severity of EUGR was classified into three categories according to the z-score of discharge weight: $z < -2.0$, <-2.5, and <-3.0. The outcomes were assessed using the Bayley Scales of Infant Development-II (BSID-II) at a corrected age of 24 months. We then estimated the association of EUGR with low mental developmental index (MDI) or low psychomotor developmental index (PDI). Multiple logistic regression and stratified analyses were used to adjust for the possible confounding factors.
Results: In total, 224 VLBW infants were enrolled in this study from 1997 to 2006. In the univariate analysis, EUGR for weight at discharge from hospital was associated with MDI <85 at the corrected age of 24 months, and this association was related to the severity of EUGR ($z < -2.5$, OR: 1.92 (1.04–3.53); $z < -3.0$, OR: 2.83 (1.26–6.36)). In addition, the relationship was not confounded by gender nor small for gestational age. The stratified analysis against hemodynamic significant patent ductus arteriosus also revealed that EUGR was an independent predictor for neurodevelopmental outcomes.

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Conclusion: In VLBW preterm infants, EUGR was significantly associated with low MDI scores assessed at a corrected age of 24 months. Early evaluation and recognition of EUGR should be emphasized when caring for preterm infants.

1. Introduction

During the last two decades, the mortality rate of preterm infants with very low birth weights (VLBW) has dropped due to better perinatal care.[1,2] However, postnatal growth retardation is still common among preterm infants,[3] with an incidence rate of extra-uterine growth retardation (EUGR) as high as 30–50%.[4,5] Preterm infants are considered to be at risk of developmental delays later in their lives,[6–8] and EUGR has been reported to be associated with the incidence of such developmental delays.[9–13] Many other factors have also been reported to contribute to such neurodevelopmental outcomes for preterm infants,[14–19] including small for gestational age (SGA), intra-ventricular hemorrhage (IVH), periventricular leukomalacia (PVL), necrotizing enterocolitis (NEC), prolonged mechanical ventilation, and neonatal seizure.

Although EUGR is regarded to be one of the risk factors in neurodevelopment, little is known regarding the role that severity and duration of EUGR might play in the neurodevelopmental outcomes among VLBW infants.[9,11] The main purpose of this study is to analyze in VLBW infants the relationship between neurodevelopmental outcomes and the severity and duration of EUGR.

2. Material and methods

Subjects were preterm infants with a birth weight <1500 gm treated in the neonatal intensive care units (NICU) of Taichung Veterans General Hospital during a 10-year period (January 1997 to December 2006). Those survived were included for our analysis. After hospital discharge, infants whose parents had agreed to participate in the follow-up study received regular growth and neurodevelopmental evaluations at the corrected ages of 6, 12 and 24 months. At each of these three time points, we recorded their body weight percentiles, Bayley Scales of Infant Development-II (BSID-II) of the Mental Developmental Index (MDI) and Psychomotor Developmental Index (PDI), neurological sequelae and performance. Basic data included weight (Wt), head circumference (HC), body length at birth and at discharge, associated comorbidities and clinical parameters as assessed and documented in medical charts by primary care physicians. The follow-up program was conducted by well-trained examiners and clinical psychologists.

We retrospective screened those VLBW infants who survived at discharge and collected data from their medical charts. Excluded subjects were infants with chromosome anomalies, hydrocephalus, neonatal seizures, congenital brain malformations, cystic PVL or severe IVH (grade III ~ IV) during hospitalization. Infants who missed the last follow-up (at the corrected age of 24 months) were also excluded.

The study protocol was approved by the Institutional Review Board (IRB) of Taichung Veterans General Hospital (approval number: CF13329B). The IRB also agreed to waive the informed consent in this retrospective observational study.

2.1. Definition of EUGR

To determine the severity of growth retardation, we classified the EUGR into three categories according to z-scores at the hospital discharge: Wt of $z < -2.0$, <-2.5, or <-3.0. The z-scores of discharge Wt were calculated based on the Taiwanese neonate intrauterine growth chart published by Hsieh et al.[20] According to the World Health Organization (WHO) growth definition,[21] underweight was defined as $z < -2.0$, and severely underweight as $z < -3.0$.

Post-discharge EUGR was defined as a Wt < 3rd percentile of the reference growth chart for Taiwanese children at the follow-up visits.[22] The growth evaluation at follow-up clinics was documented as categorized data classified according to the range of percentiles (<3, 3–10 and so on). The post-discharge EUGR was hence represented in percentiles.

Since the variances of HC and body length measurements were high, these data were not analyzed.

2.2. Z score calculation

According to reference intrauterine growth chart,[20] we calculated the Wt z-score of each infant according to the following steps: firstly, assuming a normal distribution of birth weight for each specific gestational age (GA) and gender, the GA-specific and gender-specific SD of weight was estimated by taking 1.65 as z-score (corresponding to 0.9505 on z-table[23]), 95th Wt percentile as the observed Wt and 50th Wt percentile as the mean Wt in the equation given below; secondly, Wt z-score was calculated using GA-specific and gender-specific estimated SD and 50th Wt percentile in the same equation.

$$z\ score = \frac{observed\ Wt - mean\ Wt}{SD}$$

2.3. Outcome measurements

The primary outcomes were assessed using Bayley II MDI and PDI scores at the corrected age of 24 months. Scores of MDI or PDI < 70 were taken to represent significant

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