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ORIGINAL ARTICLE

Association of Umbilical Cord Plasma Acid-labile Subunit of the Insulin-like Growth Factor Ternary Complex with Anthropometry in Term Newborns

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Background: Birth size can affect neonatal morbidity and mortality. The insulin-like growth factor (IGF) system is the most important endocrine factor influencing fetal growth. In the circulation, IGFs (mostly IGF-I) are bound to IGF-binding protein 3 (IGFBP-3) and an acid-labile subunit (ALS) to form a ternary complex. The ALS protects IGFs from decay and facilitates their endocrine activity. However, the function of ALS in fetal growth has not yet been fully determined.

Methods: Venous umbilical plasma samples were obtained from 98 term neonates and analyzed using enzyme-linked immunosorbent assays. The ALS, IGF-I, and IGFBP-3 umbilical cord plasma levels were analyzed for their association with anthropometric measurements of the neonates.

Results: The ALS, IGF-I, and IGFBP-3 cord plasma levels were positively correlated with birth weight ($r = 0.42$, $p < 0.001$; $r = 0.43$, $p < 0.001$; and $r = 0.27$, $p < 0.01$, respectively) and placental weight ($r = 0.37$, $p < 0.001$; $r = 0.31$, $p < 0.01$; and $r = 0.30$, $p < 0.01$, respectively). In addition, the ALS cord plasma levels were also positively correlated with head circumference ($r = 0.29$, $p < 0.01$). Multiple linear regression analyses showed that both ALS and IGF-I cord plasma levels were independent predictive variables for birth weight

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($p < 0.01$ and $p < 0.005$, respectively). The ALS cord plasma levels were the only independent predictive variables, however, for head circumference and placental weight ($p < 0.01$ and $p < 0.05$, respectively).
Conclusion: The ALS umbilical cord plasma levels are one important factor, in addition to IGF-I, in the IGF system for predicting birth anthropometry, at least for near-term gestation. Our results suggest that the influence of ALS on the IGF system may develop prior to birth and affect fetal growth.

1. Introduction

Birth size can affect neonatal morbidity and mortality. Large-for-gestational age neonates have a higher risk of perinatal asphyxia and birth trauma, such as clavicular fracture and brachial plexus injury.[1] Small-for-gestational age infants also have a higher risk of hypoglycemia, polycythemia, asphyxia, and abnormal neurologic symptoms in the neonatal period as well as a higher risk of long-term developmental abnormalities.[2] Moreover, birth size is even suggested to be associated with long-term adult problems, such as the amount of food intake, cardiovascular disease, and type 2 diabetes mellitus.[3,4]

The insulin-like growth factor (IGF) system is the most important endocrine factor influencing fetal growth.[5] In IGF-I or IGF-II knockout mice, the birth weights were around 60% of those of their wild-type littermates.[6] In humans, the *IGF-I* gene homozygous partial deletion caused severe intrauterine growth retardation and mutation in the promoter region of the *IGF-I* gene, which led to low IGF-I levels and low birth weight.[7,8] Studies on umbilical cord blood have also reported that IGF-I, but not IGF-II or IGF-binding protein 3 (IGFBP-3), levels are positive predictors of birth size.[9,10]

In the circulation, most of the IGF-I is bound to IGFBPs, mostly IGFBP-3, to form a binary complex, and an 85-kDa acid-labile subunit (ALS) to form a 150-kDa IGF-I—IGFBP-3—ALS ternary complex.[11] The ALS is important for stabilizing the ternary complex in the circulation.[12] It protects IGFs from decay and facilitates their endocrine activity. Free IGF-I has a half-life of 10—12 minutes, which is extended to 12—15 hours when forming a ternary complex.[13]

In a mouse model with an inactivated ALS gene (*Igfals*), mice with two null alleles ($ALS^{-/-}$) were significantly lighter than wild-type mice by 3 weeks after birth and were 13—20% lighter by 9—10 weeks after birth.[14,15] Mice with a single null allele ($ALS^{+/-}$) were only 4% lighter than wild-type mice by 10 weeks after birth. However, in both the $ALS^{-/-}$ and $ALS^{+/-}$ mice, birth weights were not significantly different from the wild type. In humans, postnatal short stature or growth failure has been reported with ALS gene mutations.[16,17] However, it is usually believed that ALS is not important for regulating fetal growth because birth weight and length are normal in most of the reported patients with an ALS gene mutation.[18,19]

In fetal circulation, ALS umbilical cord blood levels increase significantly after 25—30 weeks of gestation.[20] Previously, only one study, on a group of 81 preterm and term neonates, reported that ALS umbilical cord blood levels are one positive predictor of birth length.[21] To further explore the function of ALS in fetal growth, we measured components of the IGF-I—IGFBP-3—ALS ternary complex in umbilical cord plasma levels of term neonates to investigate their associations with birth anthropometry.

2. Materials and Methods

2.1. Newborns and plasma samples

Ninety-eight venous umbilical cord plasma samples (45 male; 53 female) were obtained from term newborns at the Chi Mei Hospital (Tainan, Taiwan) between July 2005 and January 2006. Newborns with major congenital anomalies, multiple gestation, congenital heart diseases, suspected congenital infection, and renal diseases were excluded from the study. The sample was collected using a Vacutainer tube (Becton Dickinson, Franklin Lakes, NJ, USA) containing disodium ethylenediaminetetraacetic acid and stored at 4°C immediately after the newborn had been delivered. Within 24 hours, all samples were centrifuged at 2500*g* for 15 minutes to obtain umbilical cord plasma, which was stored at −80°C until further analysis. The clinical records of the neonates were reviewed to obtain information about their gestational age, birth weight, birth length, head circumference, and sex. Their Ponderal index was calculated as 100 times birth weight in gram divided by the cube of birth length in centimeter. Gestational age at birth was calculated from the 1st day of the last menstrual period of the mother. The placental weights were obtained from information recorded by the Obstetrics Department. Term neonates were defined as having 37 or more weeks of gestation. Ethical approval was obtained from the Institutional Review Board of the Chi Mei Hospital. Consent forms were signed by the participating mothers.

2.2. Assays

The levels of IGF-I, IGFBP-3, and ALS were measured using enzyme-linked immunosorbent assays (Diagnostic Systems Laboratories, Webster, TX, USA). All samples were run in triplicate. The detection limits of the assays for IGF-I, IGFBP-3, and ALS were 0.01 ng/mL, 0.04 ng/mL, and 0.07 μg/mL, respectively. The intra-assay coefficients of variation (CV) for IGF-I, IGFBP-3, and ALS were less than 9%,