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ORIGINAL ARTICLE

Angiogenic Factors in Cord Blood of Preterm Infants Predicts Subsequently Developing Bronchopulmonary Dysplasia

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vascular endothelial growth factor

Background: Bronchopulmonary dysplasia (BPD) of prematurity is associated with impaired angiogenesis. Excess soluble fms-like tyrosine kinase-1 (sFlt-1) and lower levels of vascular endothelial growth factor (VEGF) impaired alveolarization in preterm rats. Overexpression of placenta growth factor (PlGF) in mice caused airspace enlargement, which is similar to BPD pathologically. Our study aimed to clarify whether cord blood levels of these angiogenic factors were associated with the development of BPD in preterm infants.

Methods: Preterm infants of gestational age (GA) <35 weeks who already had all the data of cord blood VEGF, PlGF, and sFlt-1 levels in our previous studies were enrolled. Cord blood levels of VEGF, PlGF, and sFlt-1 were collected. BPD was defined as the need for supplemental oxygen or mechanical ventilation support at the postmenstrual age of 36 weeks. We used the Mann-Whitney *U* test for comparison between infants with and without BPD, and multivariate analysis with logistic regression to assess the association of these molecules and the development of BPD.

Results: Infants with BPD had lower GA [(27 weeks (24–34) vs. 31 weeks (28–24)], lower birth body weight [882 g (620–1232) vs. 1538 g (886–2328)], a higher incidence of respiratory distress syndrome (RDS) (58% vs. 14%), and a higher level of PlGF [21.45 pg/dL (6.03–474.01) vs. 7.43 pg/dL (0.09–23.75)] as compared with those infants without BPD. The levels of VEGF and sFlt-1 did not differ significantly between the two groups. Multivariate logistic regression revealed that lower birth body weight ($p = 0.022$) and higher level of PlGF ($p = 0.012$) were significantly correlated with the development of BPD independently. There was no significant association between the level of VEGF or sFlt-1 and the development of BPD.

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Conclusion: Cord blood level of PlGF, rather than VEGF or sFlt-1, was significantly increased in the BPD group. Consistent with our previous report, cord blood level of PlGF may be considered as a biomarker to predict subsequently developing BPD in preterm infants.

1. Introduction

Bronchopulmonary dysplasia (BPD), a chronic lung disease followed by oxygen therapy and mechanical ventilator support, is one of the most common complications in preterm infants.[1] Indeed, it accounts for significant morbidities and mortalities for those who are born prematurely. With the introduction of antenatal steroid, exogenous surfactant, and greatly improved perinatal care, preterm infants who develop BPD are now more immature than formerly, and their clinical courses and pathological findings are also different.[2,3] Jobe[4] brought up the concept of "New BPD", which indicated that arrest of lung development instead of severe lung damage may presently be the major mechanism of BPD.

The causes of lung development arrest have been widely investigated. In recent years, ever more evidence and studies have suggested that appropriate angiogenic status is required for adequate pulmonary vascular development that could support normal alveolar lung growth.[5–7] Recently, Abman[8] proposed a vascular hypothesis that disruption of angiogenesis during lung development could impair normal lung growth including decreased alveolarization and decreased pulmonary arterial density, which were the typical characteristics of new BPD.

Vascular endothelial growth factor (VEGF) signaling is important for lung development. Inhibition of VEGF signaling led to abnormal pulmonary vascular growth and impaired alveolarization in several animal studies.[5,6,9–11] By contrast, excessive amniotic soluble fms-like tyrosine kinase-1 (sFlt-1), an endogenous VEGF antagonist contributing to the pathogenesis of preeclampsia, was documented to reduce alveolar number and arterial density in preterm rats.[9] In addition, placental growth factor (PlGF), a member of the VEGF family, mediates angiogenesis by modulating VEGF activity through competing to bind Flt-1. Besides its angiogenic effect, we found that overexpression of PlGF in transgenic mice resulted in increasing alveolar type II cell apoptosis that caused enlarged airspace and pulmonary emphysema, which is similar to BPD pathologically.[12] The aim of this study was to determine whether cord blood levels of these angiogenic or antiangiogenic factors were associated with the development of BPD.

2. Methods

2.1. Study participants

In our previous studies,[13–15] we studied the association between PlGF level of cord blood and the incidence of BPD,[13] VEGF level and the incidence of respiratory distress syndrome (RDS),[14] and sFlt-1 level and the platelet count in preterm infants.[15] Cord blood was collected using a heparinized syringe during delivery. After 15 minutes of centrifugation, the levels of VEGF, PlGF, and sFlt-1 were measured using a standardized sandwich enzyme-linked immunosorbent assay method as previously described.[13–15] In this study, preterm infants who were born less than gestational age (GA) of 35 weeks and who already had all the data of cord blood levels of VEGF, PlGF, and sFlt-1 from our previous studies, were enrolled. We excluded those infants with either prenatal maternal infection or neonatal infection within 3 days after birth. GA was defined by the means of last menstrual age or ultrasonography exams. Prenatal steroids were routinely administered during GA of 24 to 34 weeks when preterm labor was possible. We defined (RDS) as acute respiratory distress due to insufficiency of surfactant in the group of prematurity requiring higher concentration of oxygen and respiratory support based on radiographic characteristics. Under this condition, exogenous surfactant was administered via an endotracheal tube as quickly as possible when a fraction of >40% oxygen was required to maintain the blood oxygen level (SpO_2) up to 90%. As for BPD, the definition was the necessity for supplemental oxygen or any kind of ventilator support at postmenstrual age 36 weeks. We also collected all demographic information and perinatal history from a detailed chart review.

2.2. Data analysis

We used the Mann-Whitney *U* test for comparison between preterm infants with and without BPD, and multivariate analysis with logistic regression to assess the association of these molecules and the development of BPD.

3. Results

In total, 56 preterm infants were included in this study. Nineteen (34%) infants developed BPD. The BPD group had lower GA [27 weeks (24–34 weeks) vs. 31 weeks (28–24 weeks), $p < 0.001$], lower birth body weight [882 g (620–1232 g) vs. 1538 g (886–2328 g), $p < 0.001$], higher incidence of antenatal steroid usage (89% vs. 56%, $p = 0.012$), higher incidence of RDS (58% vs. 14%, $p = 0.001$), and longer period of intubation [27 days (0–109 days) vs 0 days (0–24 days), $p < 0.001$]. In addition, the BPD group had a higher level of PlGF as compared with those infants without BPD [21.45 pg/dL (6.03–474.01 pg/dL) vs. 7.43 pg/dL (0.09–23.75 pg/dL), $p < 0.001$]. However, the