Pediatrics and Neonatology (2016) xx, 1–7

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: http://www.pediatr-neonatol.com

ORIGINAL ARTICLE

Correlates of Elevated Interleukin-6 and 8-Hydroxy-2′-Deoxyguanosine Levels in Tracheal Aspirates from Very Low Birth Weight Infants Who Develop Bronchopulmonary Dysplasia

Chien-Chou Hsiao [a,b], Jui-Chih Chang [c], Lon-Yen Tsao [a], Rei-Cheng Yang [a], Hsiao-Neng Chen [a,d], Cheng-Han Lee [a], Ching-Yuang Lin [e], Yi-Giien Tsai [a,b,d,*]

[a] *Department of Pediatrics, Changhua Christian Children's Hospital, Changhua City, Taiwan*
[b] *School of Medicine, Kaohsiung Medical University, Kaohsiung City, Taiwan*
[c] *Vascular and Genomic Research Center, Changhua Christian Hospital, Changhua City, Taiwan*
[d] *School of Medicine, Chung Shan Medical University, Taichung City, Taiwan*
[e] *Department of Pediatrics, Children's Hospital, China Medical University, Taichung City, Taiwan*

Received Jul 30, 2015; received in revised form Dec 12, 2015; accepted Jan 8, 2016
Available online ■ ■ ■

Key Words
8-hydroxydeoxyguanosine;
bronchopulmonary dysplasia;
premature infant

Background: Bronchopulmonary dysplasia (BPD) remains the most common complication of very low birth weight (VLBW) preterm infants, and inflammatory regulation plays a role in the development of the BPD. Interleukin-6 (IL-6) has an important role in airway inflammation and therefore can be used as a marker of airway injury. The study aimed to compare the changes between IL-6 and oxidative stress marker with 8-hydroxy-2′-deoxyguanosine (8-OHdG) from serum and tracheal aspiration (TA) in VLBW preterm infants following development of BPD.

Methods: This birth cohort study enrolled 80 VLBW preterm infants, including 26 who developed BPD. All infants completed the study and survived at 36 weeks postmenstrual age. IL-6 and 8-OHdG concentrations from serum and TA on Day 1 and Day 28 after birth were measured using immunoassay.

Results: IL-6 and 8-OHdG in serum and TA were higher in the BPD group than in the non-BPD group on the 1st day after birth ($p < 0.05$). The IL-6 and 8-OHdG levels in TA fluid were persistently increased on the 28th day of life in the BPD group ($p < 0.05$). The TA IL-6 was positively

* Corresponding author. Department of Pediatric, Changhua Christian Children Hospital, Number 135, Nanshiao Street, Changhua City 500, Taiwan.
E-mail address: 107239@cch.org.tw (Y.-G. Tsai).

http://dx.doi.org/10.1016/j.pedneo.2016.01.004

Please cite this article in press as: Hsiao C-C, et al., Correlates of Elevated Interleukin-6 and 8-Hydroxy-2′-Deoxyguanosine Levels in Tracheal Aspirates from Very Low Birth Weight Infants Who Develop Bronchopulmonary Dysplasia, Pediatrics and Neonatology (2016), http://dx.doi.org/10.1016/j.pedneo.2016.01.004

correlated with 8-OHdG levels on the 1st day ($r = 0.64$, $p < 0.05$) and 28th day of life ($r = 0.76$, $p < 0.05$). Based on receiver operating characteristic curves as a predictor of BPD development, TA IL-6 (cutoff, 456.8 pg/mg) had 81.5% sensitivity and 77.8% specificity, whereas TA 8-OHdG (cutoff, 4.4 ng/mg) had a sensitivity of 81.5% and a specificity of 64.4%.
Conclusion: Persistent inflammation with oxidative DNA damage in the respiratory tract may be a crucial mechanism in BPD.

1. Introduction

As neonatal intensive care has improved in the past 40 years, the survival rate of premature infants has also significantly increased.[1] Bronchopulmonary dysplasia (BPD) remains the most common complication of very low birth weight (VLBW) preterm infants, causing long-term pulmonary complications and large financial burdens on the society and families.[2] BPD is a chronic lung condition and the pathogenesis of BPD had been linked to immature lung tissue, barotrauma resulting from mechanical ventilation, oxidant injury, and proinflammatory mediators with inflammation, enlarged airspaces, thick septal walls, and abnormal development of alveolar capillaries.[3,4]

Oxidative stress clearly occurs early in pregnancy and continues in the postnatal period. Preterm infants have decreased antioxidant defenses in response to oxidative challenges because they exhibit accelerated production of free radicals and limited antioxidant protection.[5] Thus, premature infants are more sensitive to oxidative stress damage in the lung, especially when supplemental oxygen or ventilator support is delivered for long periods.[6–8]

Several studies demonstrated that elevated levels of several inflammatory cytokines and chemokines in the serum and lungs cytokines of preterm neonates during the 1st week of life were associated with the development of BPD.[9–11] Fetal inflammatory response syndrome (FIRS) was originally defined as an elevation of the fetal plasma interleukin-6 (IL-6) concentration, and it was characterized by systemic activation of the fetal immune system with risk factors for BPD.[12,13] IL-6 was the major proinflammatory cytokine mediating acute lung injury and exacerbating ventilator-induced lung injury.[14–16] High IL-6 cytokine concentrations in tracheal aspirates and umbilical cord plasma of extremely low birth weight infants are considered to be an independent risk factor for BPD.[17–19]

Oxidative stress causes DNA, lipid, and protein damage. Guanine is the DNA base most prone to oxidation, both in the nucleus and in mitochondria. Upon oxidation, a hydroxyl group is added to the C-8 position of the guanine molecule, resulting in 8-hydroxy-20-deoxyguanosine (8-OHdG), one of the most common forms of free radical-induced lesions of DNA.[20] Recently, 8-OHdG has been used widely as a biomarker for the measurement of endogenous oxidative DNA damage.[8,20,21]

Oxidative stress and proinflammatory processes are strongly related, and oxidative stress may have a worse effect on inflammation of premature lungs.[22] So far, only a few studies have been conducted on inflammatory cytokines and oxidative marker from tracheal aspirates in BPD development among VLBW neonates. This study assessed the relationship between 8-OHdG and IL-6 levels from serum and tracheal aspiration (TA) and development of BPD among VLBW infants. These findings may provide further evidence to promote specific therapeutic approaches to BPD.

2. Material and methods

2.1. Patient populations

We enrolled 80 VLBW infants with gestational age (GA) of < 32 weeks and weighing < 1250 g, who were maintained on mechanical ventilation for respiratory failure in the neonatal intensive care unit (NICU) of Changhua Christian Children's Hospital, Changhua City, Taiwan. The infants were initially managed on conventional mechanical ventilators. High-frequency oscillatory ventilation was used as a rescue mode for infants not responding to conventional ventilation or those requiring high peak inspiratory pressures (> 20 cmH_2O). Relevant clinical data—such as birth weight (BW), GA, sex, cesarean delivery, Apgar score, prenatal and postnatal steroids, respiratory distress syndrome (RDS), surfactant therapy, requirement of supplemental oxygen, ventilator days, presence of sepsis, retinopathy of prematurity, patent ductus arteriosus, necrotizing enterocolitis (NEC), and intraventricular hemorrhage—were collected from the patients' chart records. BPD was defined as oxygen dependency at 28 postnatal days and at postmenstrual age of 36 weeks.[7] The primary outcome is comparing the relationship between 8-OHdG and IL-6 levels form serum and TA and development of BPD among VLBW infants. The secondary outcome is using receiver operating characteristic (ROC) curve analysis to select a cutoff value to predict BPD.

Infants were excluded from the study if they had any of the following: (1) chromosomal disorders or lethal congenital abnormalities; (2) congenital cyanotic heart disease; (3) anatomic obstructive gastrointestinal pathologies, such as intestinal malrotation with or without volvulus, stenosis, or atresia, gastroschisis, omphalocele, and Hirschsprung's disease; or (4) confirmed or family history of hereditary metabolic disorder. The same attending physician took care of the infants during their hospital stay but was blinded to their IL-6 and 8-OHdG values. The

Please cite this article in press as: Hsiao C-C, et al., Correlates of Elevated Interleukin-6 and 8-Hydroxy-2′-Deoxyguanosine Levels in Tracheal Aspirates from Very Low Birth Weight Infants Who Develop Bronchopulmonary Dysplasia, Pediatrics and Neonatology (2016), http://dx.doi.org/10.1016/j.pedneo.2016.01.004