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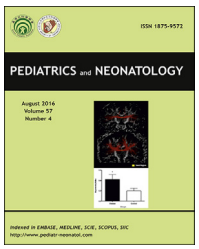

Original Article

Phenotypical characterization of human rhinovirus infections in severely premature children

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Key Words
human rhinovirus;
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prematurity;
wheezing

Background: Human Rhinovirus (HRV) has been identified as the most common cause of acute respiratory infections and hospitalizations in premature children. It is unclear if premature children are more susceptible to HRV due to their decreased pulmonary reserve or because they have enhanced lower airway reactivity to HRV.
Methods: We conducted a retrospective analysis of the clinical respiratory presentation of all PCR-confirmed HRV infections in full-term and premature children aged ≤3 years in our institution. Standardized respiratory distress scores were developed to examine lower airway obstruction (i.e., wheezing, hyperinflation, and sub-costal retractions) along with markers of decreased pulmonary reserve (hypoxemia and tachypnea) in young children with HRV infections. Demographic and clinical variables were obtained from reviewing electronic medical records (EMR).

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Results: This study included a total of 205 children; 71% of these children were born full-term (>37 weeks gestation), 10% preterm (32–37 weeks) and 19% severely premature (<32 weeks). Our results demonstrated that: 1) HRV infections in the first 3 years of life were associated with higher overall respiratory distress scores in severely premature children relative to children born preterm or full-term; 2) HRV-infected severely premature children ≤3 years old were more likely to have lower airway obstruction than HRV-infected children born preterm or full-term; and 3) other clinical signs of respiratory distress such as tachypnea and hypoxemia were not more common in severely premature than in preterm and full-term children during an HRV infection.

Conclusions: Our results indicate that HRV infections in severely premature children are associated with lower airway obstruction rather than hypoxemia or tachypnea. The latter suggests that enhanced airway reactivity is the underlying mechanism for the increased susceptibility to HRV in severely premature children. Longitudinal studies are needed to understand why premature babies develop airway hyper-reactivity to HRV and the long-term effects of early HRV infection in this population.

1. Introduction

Human rhinovirus (HRV) is the most common cause of asthma exacerbation in all ages[1] and recent evidence demonstrates that HRV causes severe respiratory infections in premature children.[2–4] In fact, HRV is the most common reason for hospitalization in this population.[4] Despite the clinical connection between HRV and prematurity, it is still unclear if premature children are more susceptible to severe HRV infections due to their underlying decreased pulmonary reserve or because premature birth itself increases the susceptibility to develop enhanced airway reactivity triggered by HRV.

Prematurity is associated with chronic lung disease (CLD) characterized by hypoxemia due to abnormal alveolarization leading to simplified gas-exchange units.[5] Interestingly, in addition to CLD, premature birth is increasingly recognized as a major risk factor for the development of the asthmatic condition,[6,7] although the underlying mechanisms of this association are presently unknown. It is also well-established that premature children are at high risk of developing severe lower respiratory tract infections caused by paramyxoviruses such as Respiratory Syncytial Virus (RSV) and Human Metapneumovirus (HMPV), which exacerbate underlying hypoxemia and CLD.[8,9] In contrast to RSV or HMPV, which have been shown to induce lung injury and increased airway oxidative stress,[10] HRV is mostly associated with the induction of Th2-driven allergic inflammation leading to airway hyperreactivity (AHR) and asthma exacerbations.[1]

The aim of this paper is to describe the clinical phenotype of HRV infections in hospitalized young children and to better understand the potential mechanisms by which this virus causes severe respiratory disease in this vulnerable population of severely premature children. Given that the pathogenic role of HRV was primarily limited to the induction and/or exacerbation of AHR in high-risk groups (e.g., asthma, COPD),[1] our hypothesis was that in the group of young children requiring hospitalization due to HRV infection, those born severely premature (<32 weeks gestational age), would have a significantly higher probability to present signs of lower airway obstruction (e.g., wheezing) and air trapping/hyperinflation (e.g., sub-costal retractions) relative to full-term individuals. In contrast, we postulated that other signs of respiratory distress not typically associated with AHR, including hypoxemia and tachypnea, would be similarly present in premature vs. full-term children hospitalized with HRV infection.

2. Materials and methods

2.1. Study subjects

We conducted a retrospective cross-sectional analysis of a cohort of children ≤3 years of age admitted with HRV infection, confirmed by PCR analysis, to the Children's National Medical Center (CNMC) in 2014. Viral PCR was performed on subjects who presented to the hospital with suspected viral respiratory tract infection at the discretion of the clinician. We included children with positive PCR for HRV and excluded individuals with mixed viral infections (HRV mixed with other viruses) to only focus on HRV. Patients with significant co-morbidities such as cardiorespiratory conditions (other than prematurity), genetic syndromes and immunosuppression were excluded from the study. This study was approved by the Institutional Review Board at the Children's National Medical Center.

2.2. Clinical and demographic variables

Clinical and demographic variables were obtained by reviewing electronic medical records (EMR) at CNMC. Demographic variables comprised gestational age in weeks, age, gender, and ethnicity. Other clinical variables included tachypnea, retractions, abnormal breath sounds (wheezing), oxyhemoglobin saturation values by pulse oximetry (SaO2), and supplemental oxygen (O2) requirement relative to patient's baseline. For the purpose of the study, clinical parameters were characterized as binary outcomes for the following: severe prematurity defined *a priori* by a gestational age of less than 32 weeks to include extremely preterm and very preterm subjects based on World Health

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