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When a common cold may trigger early supportive care

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Human rhinovirus (HRV), the culprit behind most colds, is the leading cause of hospitalization for premature babies. However, in very preterm children, exactly how HRV causes severe respiratory disease—and which patients may need more intensive observation and treatment—is less well understood.

A new study led by Children's National Health System research-clinicians showed in children who were born severely premature, HRV infections seem to trigger an airway hyper-reactivity (AHR) type of disease, which leads to wheezing and air-trapping (hyperinflation) and more severe respiratory disease. This, in turn, increases the risk for hospitalization.

The study, published online Oct. 21, 2017 in *Pediatrics and Neonatology*, found that other signs of respiratory distress, such as low arterial blood oxygen or rapid shallow breathing, were no more common in severely premature children (less than 32 weeks of gestational age) than in kids born preterm or full-term. The findings have implications for administering supportive care sooner or more intensively for severely premature children than for other infants.

"When it comes to how they respond to such infections, severely premature children are quite different," says Geovanny Perez, M.D., a specialist in pulmonary medicine at Children's National and lead study author. "We've known they are more susceptible to human rhinovirus infection and have more severe disease. However, our study findings

suggest that severely premature kids have an 'asthma' type of clinical picture and perhaps should be treated differently."

The study team sought to identify clinical phenotypes of HRV infections in young children hospitalized for such infections. The team theorized that severely premature babies would respond differently to these infections and that their response might resemble symptoms experienced by patients with asthma.

"For a number of years, our team has studied responses to viruses and prematurity, especially HRV and asthma," Dr. Perez says. "We know that premature babies have an immune response to HRV from the epithelial cells, similar to that seen in older patients with asthma. But we wanted to address a gap in the research to better understand which children may need closer monitoring and more supportive care during their first HRV infection."

In a retrospective cross-sectional analysis, the study looked at 205 children aged 3 years or younger who were hospitalized at Children's National in 2014 with confirmed HRV infections. Of these, 71 percent were born full-term (more than 37 gestational weeks), 10 percent were preterm (32 to 37 gestational weeks) and 19 percent were severely premature (less than 32 gestational weeks).

Dr. Perez and his team developed a special respiratory distress scoring system based on physical findings in the children's electronic medical records to assess the degree of lower-airway obstruction or AHR (as occurs in asthma) and of parenchymal lung disease. The physical findings included:

- Wheezing;
- Subcostal retraction (a sign of air-trapping/hyperinflation of the lungs), as can occur in pneumonia;

- Reduced oxygen levels (hypoxemia); and
- Increased respiratory rate (tachypnea).

The research team assigned each case an overall score. The severely premature children had worse overall scores—and significantly worse scores for AHR and hyperinflated lungs relative to children born late preterm or full-term.

"What surprised us, though, in this study was that the phenotypical characterization using individual parameters for parenchymal lung disease, such as hypoxemia or tachypnea, were not different in severe preterm children and preterm or full term," says Dr. Perez. "On the other hand, our study found that severely preterm children had a lower airway obstruction phenotype associated with retractions and wheezing. Moreover there was a 'dose effect' of prematurity: Children who were born more premature had a higher risk of wheezing and retractions."

Among the implications of this study, Dr. Perez sees the potential to use phenotypical (clinical markers, such as retractions and wheezing) and biological biomarkers to better personalize patients' treatments. Dr. Perez and his team have identified biological biomarkers in nasal secretions of children with rhinovirus infection that they plan to combine with clinical biomarkers to identify which patients with viral infections will benefit from early supportive care, chronic treatments or long-term monitoring.

Dr. Perez says further research in this area should pursue a number of paths, including:

- A longitudinal study to elucidate which children will benefit from asthma-like treatment, such as bronchodilators or corticosteroids;
- A study of biomarkers, including microRNAs and other

inflammatory molecules; or

- Alternatively, a longitudinal study exploring the mechanism by which wheezing develops, perhaps looking at first and subsequent rhinovirus infections in babies born at different gestational ages.

More information: Geovanny F. Perez et al, Phenotypical characterization of human rhinovirus infections in severely premature children, *Pediatrics & Neonatology* (2017). DOI: 10.1016/j.pedneo.2017.04.008

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