Why is the coronavirus infection usually mild in children? Here's a new clue

May 29 2020, by Marie McCullough

Credit: CC0 Public Domain

One of the biggest mysteries of the new coronavirus is its relative

harmlessness in most children who get infected.

At least part of the explanation may be in the cells lining their noses, according to a new study by researchers at the Icahn School of Medicine at Mount Sinai in New York City.

The researchers started with archived samples of cells from the nasal lining, or epithelium, of people ages 4 to 60. Then they measured the activity of a gene that directs production of ACE2, a protein that helps coronavirus enter the body. It turned out that ACE2 gene "expression"—the DNA instructions that are converted into a functional molecule—was lower in young children, and that expression increased with age.

"Few studies have examined the relationship between ACE2 in the airway and age," the team wrote in a letter published in *JAMA* Network. "The results from this study show age-dependent expression of ACE2 in nasal epithelium, the first point of contact for (the coronavirus) and the human body. "

The implications of that are intriguing, but not yet clear, said Ishminder Kaur, an epidemiologist and infectious-disease specialist at St. Christopher's Hospital for Children in Philadelphia. The reduced ACE2 gene expression in children suggests, but doesn't prove, that children create less of the protein that the virus uses as its gateway, or receptor.

"It's a signal, but does that translate to lower protein production, or less receptor activity?" Kaur asked. "Like any good study, it generates its own set of questions."

ACE2 (short for angiotensin converting enzyme 2) is part of a complex system that regulates blood pressure, fluid, and mineral balance in the body. Because ACE2 also helps the coronavirus take hold in the nose,

lungs, and other organs, it has become a subject of interest. For example, researchers are studying whether common blood pressure medicines that stimulate ACE2 can make COVID-19 more deadly—or less so because ACE2 tamps down inflammation and tissue scarring.

The mystery of COVID-19 in children has been as puzzling as it is a relief. Children, who make up fewer than 2% of identified cases, generally have mild symptoms or none, and rarely die of the infection.

That's the opposite of the seasonal influenza, which can be devastating in young children because their immune systems have not matured, and they don't have prior exposure to most flu strains. Flu vaccination is recommended to protect them.

But immune response may be just part of the puzzle.

To see whether the ACE2 gene may play a role, the Mount Sinai team used nasal lining samples that were provided by 305 people for a study conducted between 2015 and 2018. Half of them had asthma, which was the focus of the study.

The samples were categorized by age—children under 10, children 10 to 17, young adults 18 to 24, and adults 25 and over. ACE2 gene activity was lowest in children under 10, and rose steadily and significantly with age. (The results were statistically adjusted to make sure asthma didn't skew them.)

Although the researchers, led by pediatrician Supinda Bunyavanich, found ACE2 gene expression was linked to age, they noted that a study conducted before the pandemic of patients with severe respiratory distress found no link between ACE2 protein activity and age. However, that study didn't examine gene expression, and "the lung and nasal environments are distinct, with known differences in gene expression."

Even if the new study helps answer a basic question about pediatric COVID-19, more questions are arising. Late last month, British authorities warned about a rare but severe inflammatory syndrome in young children that appears to be a delayed complication of COVID-19 infection. Now, pediatricians around the world, including Kaur at St. Christopher's, are recognizing and reporting what is being called "pediatric multi-system inflammatory syndrome temporally associated with COVID-19.?

"Our understanding of the coronavirus is constantly evolving," Kaur said.