Researchers uncover mechanism related to severe post-COVID-19 disease in children

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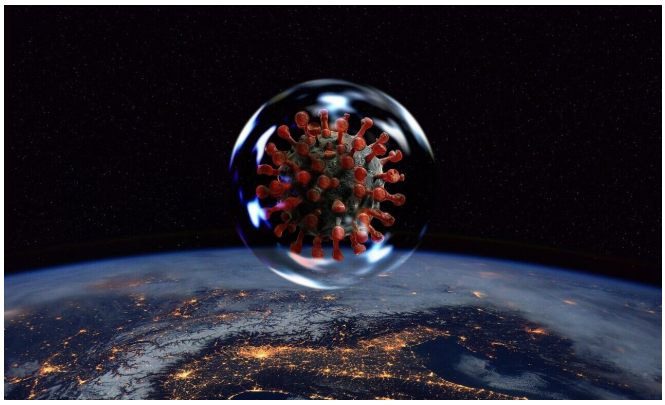

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A multidisciplinary team from MassGeneral Hospital for Children (MGHfC), Brigham and Women's Hospital and other institutions have identified the mechanism of how an extremely rare but serious post-COVID-19 complication develops in children and adolescents. Led by MGHfC pediatric pulmonologist Lael Yonker, MD, researchers determined that viral particles remaining in the gut long after an initial COVID-19 infection can travel into the bloodstream, instigating the condition called Multisystem Inflammatory Syndrome in Children (MIS-C).

The syndrome can occur several weeks after an initial infection; symptoms include high fever, abdominal pain, vomiting, diarrhea, rash and extreme fatigue. The hyperinflammatory response and "cytokine storm" seen in MIS-C can lead to extensive damage in the heart, liver and other organs.

Eighty percent of children hospitalized with MIS-C develop severe cardiac pathology and face a prolonged hospital stay and extensive recovery period. Current treatment strategies include an aggressive, long-term course of steroids and intravenous immunoglobulin.

MIS-C occurs in less than 1 percent of children with confirmed SARS-CoV-2 infection. As of May 3, 2021, the U.S. Centers for Disease Control and Prevention reported 3,742 children diagnosed with MIS-C and 35 deaths. U.S. statistics are skewed heavily toward Latino and Black children, with a total of 63 percent in cases with race or ethnicity listed.

In their recent study published in the *Journal of Clinical Investigation*, which included 100 children (19 with MIS-C, 26 with COVID-19, and 55 healthy controls), the researchers provide insight into the mechanics of MIS-C and identify potential biomarkers for early disease detection, treatment and prevention. They also describe the successful treatment of a 17-month-old infant with MIS-C.

"When we realized that 95 percent of the children with MIS-C had SARS-CoV-2 viral particles in their stool but no or low levels of particles in their noses or throats, we investigated further and found that viral material lingering in the gut long after the first COVID-19 infection could lead to MIS-C," says Yonker, lead author of the paper. The team hypothesized that SARS-CoV-2 viral particles found in the gastrointestinal tract of children move into the bloodstream, leading to the hyperinflammatory immune response characteristic of MIS-C. "This is the first study showing viral particles in the blood of MIS-C coinciding with the hyperinflammatory response," says Yonker.

Co-senior author Alessio Fasano, MD, head of MGHfC's Division of Pediatric Gastroenterology and Nutrition, is an expert on the mechanics of intestinal immune responses to pathogens. In 2000, Fasano and his team at the University of Maryland School of Medicine discovered zonulin, a protein that regulates intestinal permeability by opening the tight junctions between gut epithelial cells in the small intestine.

This opening of the spaces between epithelial cells allows the passage of substances from the gut lumen into the bloodstream, including gluten, which can cause symptoms for people genetically predisposed to celiac disease. In the early 2000s, Fasano developed larazotide acetate to work as a zonulin blocker in the treatment of celiac disease.

Prior to the advent of COVID-19, Fasano and Moshe Arditi, MD, director of the Infectious and Immunological Diseases Research Center at Cedars-Sinai in Los Angeles, co-authored a paper about a study on Kawasaki disease, a condition very similar to MIS-C, in which they showed that mice with elevated zonulin levels could be successfully treated with larazotide acetate. Subsequently, Arditi, Yonker and Fasano showed that the immune response in MIS-C is consistent with superantigenic activation. "The large spike protein—the superantigen—basically holds onto a T-cell and makes it fire off a continuous immune response," says Yonker.

In the current study, the researchers measured high levels of SARS-CoV-2 virus in the stools and high levels of zonulin in the blood of children with MIS-C. When they subsequently found viral particles in the blood, Fasano suggested the use of larazotide acetate as a therapeutic. Encouraging preliminary data on the efficacy of larazotide acetate in treating the first case of MIS-C, after obtaining compassionate use permission from the Food and Drug Administration, opened up the possible use of larazotide acetate as the first oral treatment for COVID-19 and its complications.

"Our hypothesis was that larazotide would reduce the hyperinflammation by closing the tight junctions and preventing the large spike proteins of the SARS-CoV-2 virus from entering the bloodstream," says Fasano.

Adds Yonker: "Our next plan is to develop a clinical trial to study the effect of larazotide on clinical outcomes in MIS-C. To go from characterizing a new disease, to understanding its cause, to identifying a possible new treatment is just incredible."

More information: Lael M. Yonker et al, Multisystem inflammatory syndrome in children is driven by zonulin-dependent loss of gut mucosal barrier, *Journal of Clinical Investigation* (2021). DOI: 10.1172/JCI149633

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