Medical Xpress

Study identifies genetic risk for hyperinflammatory disorder from viral infection

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A group of people with fatal H1N1 flu died after their viral infections triggered a deadly hyperinflammatory disorder in susceptible individuals with gene mutations linked to the overactive immune response, according to a study in *The Journal of Infectious Diseases*.

Researchers at Cincinnati Children's Hospital Medical Center, the University of Alabama Birmingham (UAB) and Children's of Alabama led the study, posted online Nov. 23. They suggest people with other types of infections and identical gene mutations also may be prone to the disorder, known as reactive HLH (rHLH), or hemophagocytic lymphohistiocytosis.

HLH causes the immune system to essentially overwhelm the body with inflammation that attacks vital organs, often leading to death. Study authors raise the possibility of screening children for HLH genes to identify those who may be at risk during a viral infection.

"Viruses that cause robust immune responses may be more likely to trigger rHLH in genetically susceptible people," said Randy Cron, MD, PhD, a senior investigator on the study and physician in Pediatric Rheumatology at UAB and Children's of Alabama. "Prenatal screening for mutations in common HLH-associated genes may find as much as 10 percent of the general population who are at risk for HLH when an inflammation threshold is reached from H1N1 or other infectious

triggers."

This study is the first to identify mutations of HLH-associated genes in H1N1 cases where patients had clinical symptoms of rHLH and a related condition called macrophage activation syndrome (MAS). An outbreak of H1N1 in 2009 turned into a global pandemic. H1N1 has since become part of the viral mix for the annual flu season and preventive vaccine, the authors note.

Collaborating on the study were co-senior investigator Alexei Grom, MD, and first author Grant Schulert, MD, PhD, both physicians in the Division of Rheumatology at Cincinnati Children's.

Cron and Grom have published articles linking clinical signs of rHLH to patients with hemorrhagic fever and systemic juvenile idiopathic arthritis (an inflammatory condition in which the body thinks it has an infection and attacks vital organs and joints). The precise reasons these patients have clinical signs of rHLH have not been clear, although some juvenile arthritis patients who develop MAS also have HLH-linked gene mutations, according to the authors.

There are two types of HLH, hereditary and the reactive form focused on in the current study. Both share common physical traits that involve the body's immune system overheating, excessive proliferation of immune cells call macrophages and severe inflammation. The only curative treatment at present is a bone marrow transplant, a risky procedure that is not always successful.

"There are no widely accepted and validated diagnostic criteria for reactive HLH, and criteria for familial HLH are not considered effective for rHLH or MAS," said Schulert. "Regardless, it seems clear that a sizeable number of patients with fatal H1N1 infection develop rHLH. Our data suggest some people may have a genetic predisposition to

develop severe H1N1 influenza, and critically ill H1N1 patients should be carefully evaluated for rHLH and MAS. The question is whether immunosuppressive therapy may benefit some patients with life-threatening influenza infection."

The current study examined the medical records of 16 adult patients, ages 23 to 61, who died between 2009 and 2014 while infected with H1N1. The patients and their HLH-like symptoms initially were identified through the Michigan Hospital Department of Pathology Database by study collaborator Paul Harms, MD, and his team at the Michigan Center for Translational Pathology, University of Michigan Medical School.

Processed tissue samples from the patients were examined using whole exome genetic sequencing, which reads the entire genetic code of every gene in a person.

Forty-four percent of the H1N1 cases met the clinical criteria for HLH and 81 percent for the related condition MAS. Five patients carried one of three different gene mutations in the commonly identified HLH gene LYST. Two of those five same patients also had a specific mutation in the gene PRF1, which decreases the function of immune system Natural Killer cells and aids the over proliferation of macrophage cells. Several patients in the study also carried variants of other genes linked to observed cases of MAS.

The current study involved a small patient population in a single state and was retrospective in design (looking at records from past cases). The authors recommend conducting a larger prospective study to determine if genomic testing can predict the course of disease progression during influenza and other types of infections. Researchers also want to conduct further genomic and biological testing of children with juvenile arthritis to solidify potential links between gene mutations and secondary

autoimmune disease.

Provided by Cincinnati Children's Hospital Medical Center