Off-target immune response could predict COVID-19 severity

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The presence of special immune system defense molecules, called autoimmune antibodies, has been strongly tied to how poorly people fare when hospitalized with COVID-19, a new study shows.

Led by researchers at NYU Grossman School of Medicine, the study detected the autoimmune antibodies in the blood of more than a third of men and women on admission to hospital and confirmed to have the disease.

Among the new study findings is that a subset of these autoimmune antibodies that bind to DNA or to a particular type of fat molecule, a lipid called phosphatidylserine, were more often twice as abundant at the start of coronavirus infection in those whose conditions worsened quickly than in those whose health did not decline. Patients with these elevated levels of autoimmune antibodies were five to seven times more likely to develop severe disease than those whose antibodies levels were stable.

People hospitalized with life-threatening cases of COVID-19, researchers say, required intensive care and a mechanical ventilator to help them breathe while those who had lower levels of these autoantibodies usually breathed on their own and largely recovered.

Publishing in the journal *Life Science Alliance* online Sept. 9, the team's latest work is based on the nature of antibodies, they explain, immune proteins that target invading bacteria and viruses. By contrast, autoimmune antibodies instead attack an infected person's own cells and molecules. This includes lipids and genetic material, or DNA, which are known to spill into the bloodstream as cells are killed by disease, such as COVID-19.

"Our study results show that initial blood levels of anti-DNA or anti-phosphatidylserine antibodies were directly linked to the severity of illness in those with COVID-19," says study co-lead investigator Claudia Gomes, Ph.D., a postdoctoral fellow at NYU Langone Health.

"While further testing is needed, our findings suggest that a test for the

presence of anti-DNA and anti-phosphatidylserine antibodies could help identify those COVID-19 patients admitted to hospital who are most at risk of needing intensive care and who need to be monitored more closely," says Marisol Zuniga, MS, also a study co-lead investigator at NYU Langone.

For the new study, researchers examined the medical records and blood tests from 115 white, Black, Asian, and Hispanic men and women hospitalized for COVID-19 at NYU Langone hospitals between April and June 2020. Roughly equal numbers had severe disease from which they either survived or died, or did not require intensive care and recovered quickly. Test results for more than 100 measurements, such as blood oxygen levels, liver enzymes, and kidney function, were compared with levels of autoimmune antibodies.

The researchers designed the analysis to learn whether common autoimmune antibodies were present in COVID-19, as other studies in other infectious diseases had already suggested, and whether or not variations in blood levels were tied to how sick people became.

Thirty-six percent of study participants were found to have autoimmune antibodies when they were admitted to the hospital. Levels of anti-DNA and anti- phosphatidylserine antibodies were then strongly linked to severity of illness. Specifically, 86 and 93 percent of patients with high levels of anti-DNA and anti- phosphatidylserine antibodies, respectively, experienced severe COVID-19. Levels of anti-DNA antibodies were also linked to increases in blood coagulation (thrombosis) and cell death (lysis), especially in muscle tissue. Researchers say both thrombosis, which can lead to life-threatening blood clots, and damage to muscle tissue, especially in the heart, have been observed in the most serious cases of COVID-19.

"Our overall observations suggest that in severe cases of COVID-19, the

production of autoimmune antibodies plays a key role in blood clotting and cell death," says study senior investigator Ana Rodriguez, Ph.D., a professor in the Department of Microbiology at NYU Langone. "Our study adds evidence to the underlying premise of the disease that the misguided immune system's response is doing more damage than the actual viral infection itself."

Rodriguez cautions that further experiments will be needed to determine if autoimmune antibodies are indeed the "cause or effect" of the blood clotting and cell lysis observed in her team's study.

If found to be causal of cell damage, new COVID-19 treatments could include antibody injections from healthy donors to dilute the presence of autoimmune antibodies. Other experimental therapies under consideration involve biodegradable antigens that attach to autoimmune antibodies and neutralize them, but do not lead to a lasting antibody immune reaction of their own.

More information: Claudia Gomes et al, Autoimmune anti-DNA and anti-phosphatidylserine antibodies predict development of severe COVID-19, *Life Science Alliance* (2021). doi.org/10.26508/lsa.202101180

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