The infection with severe acute respiratory syndrome coronavirus type-2 (SARS-CoV-2) can lead to a new disease called long-COVID-19 or post-acute COVID-19 syndrome (PACS). This syndrome can occur in various populations, including children, young adults, and those who had only mild COVID-19. Long/post-COVID represents a heterogeneous nosological entity, despite similar or overlapping symptoms between patients, and clear diagnostic criteria are yet to be established. In this pilot study, the authors from France and Spain investigated the circulating levels of envelope (ENV) proteins encoded by human endogenous retrovirus type W (HERV-W) in patients with post-COVID syndrome, as well as the relationship between the expression of HERV-W ENV proteins and levels of anti-SARS-CoV-2 immunoglobulins (Ig).

HERVs are relics derived from retroviruses that infected the human ancestral genome millions of years ago and were incorporated into the chromosomal DNA. HERVs have been vertically transmitted to offspring in a Mendelian fashion, constituting up to ~8% of the human genome. Usually, most HERVs are epigenetically silenced or silenced by a mutation. However, they may be activated under certain conditions, including irradiation, chemical exposures, or exogenous viral factors. HERV aberrant expression is associated with infectious, autoimmune, malignant, and neurological diseases.

SARS-CoV-2 is an enveloped, positive-sense, single-stranded RNA virus. Its genome encodes four structural proteins, the spike (S), envelope (E), nucleocapsid (N), and membrane (M) protein. Like other infectious agents, SARS-CoV-2 can activate dormant HERV sequences ancestrally integrated into human genomes.

About the Study and Results

The study included a total of 66 patients, 22 diagnosed with acute COVID-19, 12 diagnosed with post-COVID syndrome, 17 pre-pandemic cases of chronic fatigue syndrome, 4 pre-pandemic healthy blood donors, and 11 healthy blood donors whose samples were taken during the pandemic. Acute COVID-19 patients were admitted to the hospital with moderate to severe disease. The symptoms registered in cases diagnosed with post-COVID syndrome lasted for a minimum of six months.

Circulating HERV-W ENV proteins were found in 41% (9/22) of patients diagnosed with acute COVID-19, and 58% (7/12) of patients diagnosed with post-COVID syndrome. According to the authors, a higher proportion of HERV-W ENV expression in post-COVID cases than in acute COVID-19 cases might suggest a link between HERV-encoded proteins and post-COVID syndrome, or, more likely, with a subgroup of patients with post-COVID syndrome.

The expression of HERV-W ENV proteins in post-COVID patients was detected 6 to 19 months after the acute infection, confirming that chronic expression of HERV-W ENV proteins is possible over one year after the acute COVID-19.

Interestingly, 2/17 pre-pandemic participants with chronic fatigue syndrome, a disease with overlapping symptoms with post-COVID, were strongly positive for HERV-W ENV proteins.

In acute COVID-19 patients, the anti-SARS-CoV-2 antibody response was increased for all immunoglobulin isotypes (IgG, IgM, IgA, and IgE). 72% of patients had elevated total IgM levels and 59% had elevated total IgG, IgA, and IgE levels. As expected, pre-pandemic controls were negative for any of the anti-SARS-CoV-2 immunoglobulins.

Interestingly, in 75% of cases diagnosed with post-COVID the levels of anti-S, and anti-N IgE antibodies were elevated compared to pre-pandemic controls.

Conclusion

The authors stated that two results are important in this pilot study. The first is HERV-W ENV antigenemia in 58% of post-COVID patients long after the acute SARS-CoV-2 infection, and the second is a positive anti-SARS-CoV-2 IgE serology in 75% of cases diagnosed with

post-COVID. The authors emphasized that sustained immune response against SARS-CoV-2 antigens was unexpectedly biased towards IgE reactivity in the post-COVID group.

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