Human endogenous retroviruses (HERVs) are relics of ancient infections derived from retroviruses that infected the human ancestral genome millions of years ago and were incorporated into the chromosomal DNA. Because of such endogenization and further fixation in the human population, HERVs have been vertically transmitted to offspring in a Mendelian fashion, constituting up to ~8% of the human genome. Although HERVs were considered for a long time as part of the "junk" DNA, 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. A consortium of authors conducted this observational study to investigate a possible association between severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) and the expression of an envelope (ENV) protein encoded by human endogenous retrovirus type W (HERV-W) in a group of hospitalized psychotic patients who had no history of acute COVID infection and had not been vaccinated against SARS-CoV-2. They investigated whether patients diagnosed with psychosis spectrum disorders have increased serum levels of HERV-W-ENVs since approximately one-half of patients diagnosed with schizophrenia and one-third of patients diagnosed with bipolar disorder were found to be positive for HERV ENV proteins in their blood. Notably, there are differences in the molecular characteristics of HERV-W between schizophrenia, bipolar disorder, and multiple sclerosis. Slokar G, Hasler G. Human Endogenous Retroviruses as Pathogenic Factors in the Development of Schizophrenia. Front Psychiatry. 2016 Jan 11;6:183. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4707225/

HERVs are roughly divided into three classes: Class I comprises gamma-retroviruses, including HERV-H, and HERV-W, Class II comprises beta-retroviruses, including HERV-K

and Class III comprises foamy viruses, such as HERV-L and HERV-S. HERV-K is the most active and intact group of endogenous retroviruses within the genome of primates. HERV genome consists of four essential genes (gag, pro, pol, and env). The env gene encodes ENV protein, which was shown to be neurotoxic. Chronic viruses such as the Epstein–Barr virus induce the transcription of the HERV-K, suggesting that other viruses might also activate HERV transcription.

Recent data have shown that plasma and peripheral blood cells (T and B lymphocytes) of severe COVID-19 patients, as well as numerous *postmortem* tissues (the lungs, heart, gastrointestinal system, and brain) from deceased patients of severe acute COVID-19, were positive for HERV-W ENVs. The mean plasma titer of HERV-W ENVs in plasma progressively increased with disease severity, suggesting that HERV envelope proteins could be a potential marker of COVID-19 severity.
https://discovermednews.com/sars-cov-2-can-induce-expression-of-human-endogenous-retroviruses-w-envelope-proteins/

About the Study and Results

The study enrolled 48 hospitalized patients diagnosed with psychosis spectrum disorders and a control group of 55 caregivers without COVID-19-related symptoms. Out of 48 hospitalized patients with psychosis spectrum disorders, 38 had schizophrenia, and 10 had schizoaffective disorder. In the group of patients with psychosis spectrum disorders, 35% were women, whereas in the control group, 79 % were women. The mean age of patients was 41.7 ± 12.7 years and the control group was 42.9 ± 10.8 years.

The sera were collected during the first wave of COVID-19 in the spring of 2020 before the COVID-19 vaccination. Both groups, patients, and controls reported a negative history of COVID-19. However, a positive anti-SARS-CoV-2 serology has been detected in both groups. This indicates either a prior infection or a significant response following the exposure to SARS-CoV-2. Compared to controls, hospitalized patients with psychosis spectrum disorders had a significantly higher number of positive sera and a higher titer of specific anti-SARS-CoV-2 antibodies.

Importantly, HERV-W ENVs were detected only in participants with a positive anti-SARS-CoV-2 serology in both groups. A higher proportion of SARS-CoV-2 seropositive participants in the group of hospitalized patients with psychosis spectrum disorders (27%, 13/48) was positive for circulating HERV-W ENVs than in the control group (9%, 5/55).

Patients with psychosis spectrum disorders were categorized into three clusters based on the SARS-CoV-2 seropositivity, HERV-W ENV positivity, and the levels of proinflammatory cytokines, such as interleukin (IL)-1β, IL-6, IL-8, and tumor necrosis factor (TNF)-α. All patients in cluster 1 (17%; 8/48) were negative for SARS-CoV-2 and HERV-W ENV and had low serum levels of proinflammatory cytokines. All patients in cluster 2 (56%; 27/48), were positive for SARS-CoV-2 but negative for HERV-W ENV and had low/intermediate levels of proinflammatory cytokines. All patients in cluster 3 (27%; 13/48 participants), were positive for SARS-CoV-2 and HERV-W ENVs and had higher levels of proinflammatory cytokines TNF-α, IL-8, and IL-6 than other clusters. The levels of IL-1β differed significantly between clusters 1 and 3.

According to these findings, SARS-CoV-2 and HERV-W ENV positivity were associated with high serum levels of proinflammatory cytokines in hospitalized patients diagnosed with psychosis spectrum disorders.

Conclusion

This study demonstrated increased circulating levels of HERV-W ENV proteins and proinflammatory cytokines only in hospitalized patients for psychosis spectrum disorders who had positive anti-SARS-CoV-2 serology. The finding of HERV-W ENVs only in seropositive patients suggests a strong link between HERV-W activation, cytokine expression, and SARS-CoV-2 infection. Since the underlying mechanism remains unclear, these findings require further investigation.

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Journal Reference

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