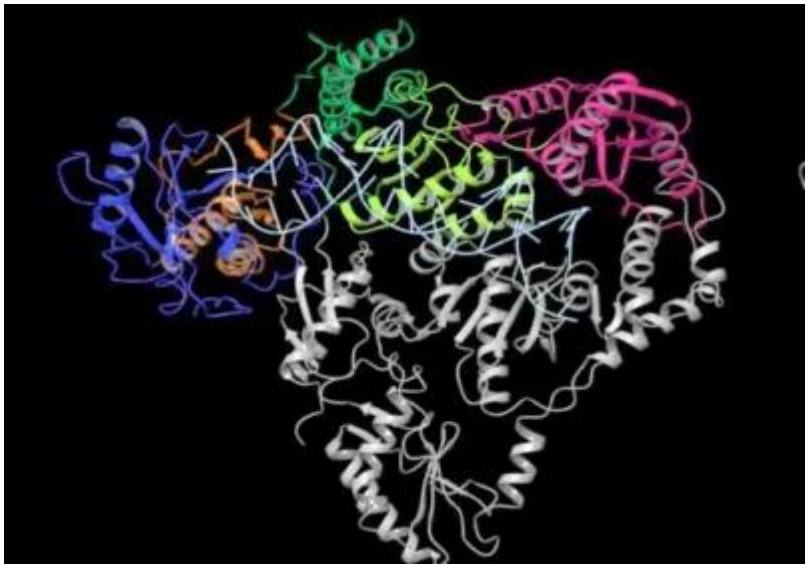
Children positive for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) are usually asymptomatic or develop mild disease. However, they are at risk of developing a postinfectious complication, multisystem inflammatory syndrome in children (MIS-C), characterized by severe systemic inflammation of multiple organs and tissues. Certain clinical characteristics of MIS-C overlap with Kawasaki disease (KD), a febrile systemic vasculitis of the small- and medium-sized arteries that usually affects children under the age of five. Therefore, MIS-C is also called Kawasaki-like syndrome. In this study, the researchers from Italy analyzed the transcriptional levels of human endogenous retroviruses (HERVs), HERV-related genes, and immune mediators in the acute COVID-19, acute, and subacute phases of KD or MIS-C, and healthy controls.

The HERVs are relics of ancient infections, characterized by an RNA intermediate, reverse-transcribed into a double-stranded DNA. This double-stranded DNA, called a provirus, can integrate into the host cell genome. Because of such a process of 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. HERVs are stable components of the human transcriptome and exhibit differential expression across a diverse range of human tissues.

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. The aberrant expression of HERVs has been associated with conditions such as infectious, autoimmune, malignant, and neurological diseases. Therefore, HERVs are regarded as “dormant enemies within”.

The authors noted that their research group and other scientists have previously demonstrated that the SARS-CoV-2 can activate HERVs, inducing inflammatory and immune reactions. A recent study has shown that SARS-CoV-2 can activate HERV type-W ENV proteins in a manner independent of the ACE2 receptor in cultured peripheral blood mononuclear cells of adult healthy blood donors. Furthermore, circulating HERV-W ENV proteins were identified in plasma or serum samples of all adult patients with severe COVID-19 admitted to the ICU, and also in various *postmortem* tissues obtained from severe COVID-19 patients, including the lungs, heart, brain, nasal mucosa, and gastrointestinal tract. https://discovermednews.com/sars-cov-2-can-induce-expression-of-human-endogenous-retroviruses-w-envelope-proteins/



About the study

This multicentre prospective study included children in the acute or subacute phase of KD, the acute or subacute phase of the MIS-C, the acute COVID-19, and healthy controls. Reverse transcription polymerase chain reaction (RT-PCR) of nasopharyngeal swabs and symptoms compatible with COVID-19 were used for SARS-CoV-2 infection diagnosis. The diagnosis of KD was made according to the guidelines of the American Heart Association in 2017. The diagnosis of MIS-C was made according to WHO criteria. The “acute phase” was defined as the time from disease onset to the 10th day of fever, while the “subacute phase” was defined as the time from the 11th to the 20th day after the fever onset. The healthy controls reported no neurological or psychiatric disorders or the presence of ongoing infections in their medical history.

The authors used qRT-PCR to assess the transcriptional levels of HERVs, HERV-related genes such as syncytin (Syn) 1 and 2, alanine/serine/cysteine/threonine-preferring transporter (ASCT) 1 and 2, major facilitator superfamily-domain containing 2A (MFSD2A), as well as mRNA levels of inflammatory and regulatory cytokines, such as interleukin (IL)-1β, IL-6, and IL-10, tumor necrosis factor-α (TNF-α), interferon (INF-γ), monocyte chemoattractant protein 1 (MCP-1), and Toll-like receptors (TLR-3, TLR-4, TLR-7. and TLR-9).

Results

The study included 54 pediatric patients and 19 healthy controls. Eight children were diagnosed with KD, 17 with MIS-C, and ten with acute COVID-19.

HERV-W, HERV-K, Syn-1, and ASCT-1 and 2 were upregulated in blood samples of pediatric patients diagnosed with all three diseases compared to healthy controls. Children with all three diseases also had higher mRNA levels of IL-1β, IL-6, IL-10, TNF-α, MCP-1, IFN-γ, and TLRs than healthy controls.

mRNA levels of Toll-like receptors TLR-3, TLR-4, and TLR-9 were increased in children in the acute phase of COVID-19, and in children in the acute or subacute phase of MIS-C. The authors explained that increased mRNA levels of TLRs parallels HERV activation in children diagnosed with COVID-19 or MIS-C.

Increased transcriptional activity of Syn-2 and MFSD2A was detected only in blood samples of pediatric patients diagnosed with MIS-C. Also, HERV upregulation correlated with cytokine expression only in patients with MIS-C. HERV-W expression correlated negatively with IL-10 levels and positively with C-reactive protein levels. Syn-2 expression and IL-10 levels correlated negatively, whereas HERV-K expression correlated positively with IL-10 levels.

Since some children infected with SARS-CoV-2 are at risk of developing a postinfectious complication MIS-C, researchers compared the blood samples of children diagnosed with these two diseases. Pediatric patients with MIS-C had higher expression of HERV-W, Syn-1 and Syn-2, ASCT-1 and 2, MFSD2A, and TNF-α than children diagnosed with COVID-19. In contrast, pediatric patients with COVID-19 had higher levels of IL-6, IL-10, MCP-1, TLR-3, and TLR-9 than patients with MIS-C.

When children diagnosed with MIS-C were compared with children diagnosed with KD, data revealed higher expression of HERV-W, HERV-K, Syn-1, Syn-2, ASCT-1, MFSD2A, and TNF-α in children in the acute phase of MIS-C than in children in the acute phase of KD. Also, children in the subacute phase of MIS-C had higher expression of HERV-K, Syn-2, MFSD2A, IL-10, and MCP-1 than children in the subacute phase of KD.

The progression of KD revealed a decrease in TNF-α, MCP-1, and IL-10 levels and increased expression of HERV-K in the subacute phase compared to the acute phase. The progression of MIS-C has shown decreased TNF-α, TLR-3, TLR-4, TLR-7, and TLR-9 levels and increased IL-6 and IL-10 levels in the subacute phase of the disease compared to the acute phase.

Conclusion

This study has shown the upregulation of HERVs, HERV-related genes, and immune mediators in the acute COVID-19, and acute, and subacute phases of KD or MIS-C. The

authors noted that this study has demonstrated, for the first time, that HERVs and Syn-1 were highly expressed in KD patients, although these levels do not reach those observed in MIS-C patients. Given the inflammatory nature of KD and the ability of HERVs to modulate the inflammatory response, researchers speculated that HERVs may contribute to the immunopathogenesis of KD. In addition, the increased mRNA levels of Syn-2 and MFSD2A seem to be a characteristic feature of MIS-C patients at the transcriptional level.

These findings support the role of HERVs in inflammatory diseases and their interaction with the immune system.

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