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The Long COVID: a new challenge for gender-specific medicine?

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Several people who have had severe to moderate or mild form of SARS-Cov-2-induced disease (COVID-19) may suffer from a huge series of variable and debilitating symptoms for many months after the initial infection, i.e. also when negative. They present a situation that, for lack of a better definition, has been called 'Long COVID', while the patients with these symptoms are called COVID 'long haulers'.[1]

In adults, the condition bears some similarity to the post-infectious syndromes that follow the Chikungunya and Ebola infections, and is characterized by long-term sequelae, persisting for more than two months after the typical COVID-19 recovery period. A plethora of different symptoms has been described so far. These include: persistent fatigue, headache, shortness of breath, anosmia (loss of smell), muscle weakness, fever, tachycardia, intestinal disorders, cognitive dysfunction (brain fog) and skin manifestations. The incidence of Long COVID in the adult population has partially been investigated taking sex into account. Women seem to be twice as likely as men to develop Long COVID, but only until around age 60, when the risk level becomes similar. In addition to being a woman, older age and a higher body mass index also seem to be risk factors for Long COVID.[2-4]

Importantly, Long COVID seems to affect the youngest patients also, i.e. Post-COVID pediatric patients. More than 25% of these subjects had at least one symptom over 120 days after the first diagnosis, and more than 20% had three or more symptoms. The most common problems were muscle and/or joint pain, headache, chest pain or a feeling of chest tightness, palpitations and sleep disturbances. However, analyzing these data, no disparity was found between young male and female patients.[5] Further, more extended studies appear mandatory in order to elucidate this point.

What are the factors responsible for this syndrome? It has been hypothesized that organ/tissue damage caused by an excessive inflammatory response activated by the virus – but also by an autoimmune reaction induced by the virus itself – could be responsible for the Long COVID symptoms. In fact, the virus may have some similarities with some 'components' of the organism (a phenomenon known as molecular mimicry). This could generate antibodies that, in the long run, could also react against the organs or tissues, causing the clinical manifestations and symptoms described. In fact, the immune response to both genetic and hormonal factors is stronger in women than in males.[6] This could represent a double-edged sword: on one hand the outcome of acute COVID-19, that appears to be more severe in men, on the other hand the autoimmune reactions that, as for several autoimmune diseases, are more frequent and harmful in females, leading – or contributing – to the occurrence of Long COVID. In fact, it was suggested long ago that viruses can contribute to the production of autoimmune antibodies. For example, Epstein-Barr virus, cytomegalovirus and human immunodeficiency virus are capable of triggering the production of autoimmune antibodies. SARS-Cov-2 could make the same, since patients with COVID-19 have been demonstrated to develop multiple types of autoantibodies. This could lead to relevant and multiple clinical manifestations of the Long COVID syndrome.[7-9]

Since the autoimmune hypothesis could justify the higher incidence of this syndrome in women, the study of the appearance of autoantibodies in patient serum and the characterization and specificity of these autoantibodies should be mandatory as an important initial step in identifying personalized and specific treatments also based on the sex of the patients affected by Long COVID.

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