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Letter to the Editor

Neurotropism of SARS-CoV 2 and others Coronavirus in Children: Mechanisms and Clinical Manifestations

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The new coronavirus disease 2019 [COVID-19], which emerged in December 2019 in Wuhan, a city of the People's Republic of China, is responsible for the well-known 2019-2020 coronavirus pandemic that affected the entire world population. COVID-19, and later named SARSCoV-2 [Severe Acute Respiratory Syndrome, Coronavirus , type 2] by the International Committee on Taxonomy of Viruses [ICTV] and rapidly sequenced, recorded and demonstrated human transmission. SARCCoV-2 [belonging to the β-coronavirus (βCoVs) subgroup], along with H5N1 [hemagglutinin 5, NA subgroup 1] influenza A, H1N1 [haemagglutinin 1, NA subtype 1] 2009 and Middle Eastern respiratory syndrome coronavirus [MERS-CoV] they cause acute lung injury (ALI) and acute respiratory distress syndrome (ARDS), up to lung failure with possible fatal outcome.[1,2] From the studies in the literature and, by now, from the world experience of individual COVID-19 centers, it emerges that the symptoms of affected individuals are not limited exclusively to the respiratory system.[3] Clinical manifestations are typical flu-like signs/symptoms but nevertheless, headache, diarrhea, skin lesion, nausea, vomiting and anosmia, configuring an intrinsic neurotropic feature of the virus.[4,5] What is unclear is whether SARSCoV-2 directly affects neuronal cells by inducing damage, which in turn can cause refractoriness to treatment. Neurotropism has been demonstrated in members of the CoVs family.[6-16]

Much of the information on the transmission of SARSCoV-2 is gleaned from the knowledge we have about the CoVs. However, it cannot be excluded that there are differences. The human-to-human transmission modes of SARSCoV-2 are by: air, through droplets; direct contact; fecal-oral. Studies confirm the possibility of transmission even through contaminated surfaces and/or objects.[17] The vertical mother-child transmission remains doubtful.[18] Pathophysiological hypotheses SARSCoV-2 disease infects humans regardless of age. However, pediatric cases in the literature are rare. The reason for the low pediatric susceptibility to the virus is unclear. In addition to this, most infections in children manifest clinically with different characteristics than adults. SARSCoV-2 shares with the SARS coronavirus, the same input receptor as the host cell, the angiotensin-converting enzyme 2 [ACE2], which binds to the S-glycoprotein located on the outer surface of the CoVs, which in turn viral entry into host cells.[19,20] There is a correlation between ACE2 expression and SARS-CoV infection in vitro.

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The level of expression and pattern of expression of human ACE2 in different tissues and at different ages could define the sensitivity, symptoms and outcome of SARSCoV-2 infection. Other hypotheses aimed at explaining the lower susceptibility to SARSCoV-2 infection in pediatric age and the differences in clinical manifestations between children and adults, such as immaturity of the innate versus adaptive immune system in children. Few data in the literature for respiratory damage and even more for neurological damage in pediatric age. The data present in the literature mostly concern adults. The mechanisms by which SARSCoV-2 cause neurological damage are manifold, such as direct damage to specific receptors, cytokine mediated lesions, retrograde along the nerve fibers.[21] Just as ACE2 is expressed on lung epithelial cells in the same way it seems to be expressed by endothelial cells of the blood-brain barrier, telling through vascular damage the entry of the virus into the nervous system. Furthermore, virus binding appears to generate a global systemic inflammatory response (SIRS), producing increased levels of interleukin (IL) -6, IL-12, IL-15 and tumor necrosis factor alpha (TNF -α); activation of glial cells; producing a massive pro-inflammatory state of the central nervous system. Notably, IL-6 levels were correlated with the addition of sarsCoV2 disease severity.[21,22] These systemic effects combined with localized pulmonary alveolar damage cause severe hypoxia, which can lead to cerebral vasodilation and cerebral edema and ischemia. Finally, SARSCoV-2 can travel retrograde along the olfactory nerve and the bulb, communicate a communication between the nasal epithelium and the central nervous system, this for example could be the basis of the common anosmia disorder.[22,23] The prevalence of neurological symptoms in SARSCoV-2 patients became more evident. According to the literature, pre-existing neurological conditions such as previous cerebrovascular accidents and Parkinson's disease portend worse outcomes, as well as the incidence of neurological complications secondary to SARSCoV-2 infection is higher. However, the neurotropism of SARSCoV-2 is currently being studied to account for the devastating brain stem-mediated complications in both the cardiovascular and pulmonary systems.

The main clinical manifestation of SARSCoV-2 infection concerns the respiratory system. However, due to the growing number of cases and related studies, clinical manifestations are described with neurological syndromes secondary to infection such as meningitis, encephalitis, encephalopathy, Giullian-Barré syndrome, as well as signs and symptoms such as headache, dizziness, lipothymia, hyposmia, hypogeusia. Therefore the neurological symptoms from SARSCoV-2 have been divided into three categories: central nervous system (dizziness, headache, loss of consciousness, convulsions, acute cerebrovascular disease, loss of muscle coordination); peripheral nervous system (anosmia, ageusia, visual disturbances, neuralgia); injury to the skeletal muscles, which are in contact with the nerve fibers that carry information related to movements and senses.[25-28]

The new coronavirus disease 2019 [COVID-19], is responsible for the pandemic that affected the entire world population. The main clinical manifestation of SARSCoV-2 infection concerns the respiratory system. However, clinical manifestations are described with neurological syndromes secondary to infection such as meningitis, encephalopathy, Giullian-Barré syndrome, as well as signs and symptoms such as headache, lipothymia, hyposmia, hypogeusia. The neurological symptoms from SARSCoV-2 have been divided into three categories: central nervous system (dizziness, headache, loss of consciousness, convulsions, acute cerebrovascular disease, loss of muscle coordination); peripheral nervous system (anosmia, ageusia, visual disturbances, neuralgia); injury to the skeletal muscles, which are in contact with the nerve fibers that carry information related to movements and senses.

Probably in children, as in adults, respiratory distress is not only the result of lungs inflammatory structural damage. It is also due to damage caused by the virus in the respiratory centers of the brain, with his neurotropism or by autoimmune system involvement as SARSCoV-2 infection can be a trigger of the disorders. Furthermore, it appears that SARSCoV2 infection in children manifests itself as neurological disease or manifestations of neurological involvement without affecting the respiratory system and/or other organs.

This supports the thesis that, as in adults, in children respiratory distress is not only the result of lungs inflammatory structural damage. It is also due to damage caused by the virus in the respiratory centers of the brain, with his neurotropism. Furthermore, it appears that SARSCoV2 infection in children manifests itself as neurological disease or manifestations of neurological involvement without affecting the respiratory system and/or other organs. Other studies need to be done to better specifies this issue.

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