Letter: Incidence, Characteristics, and Outcomes of Large Vessel Stroke in COVID-19 Cohort: An International Multicenter Study

To the Editor:

We read with great interest the article by Khandelwal et al[1] titled "Incidence, Characteristics, and Outcomes of Large Vessel Stroke in COVID-19 Cohort: An International Multicenter Study." The authors have meticulously conducted a cross-sectional retrospective, multicenter study, to determine the incidence of acute ischemic stroke with large vessel occlusion (LVO) in patients with the coronavirus-19 disease (COVID-19), in 12 centres specialized in the management of neurovascular diseases. It was found that of 6698 patients with COVID-19 admitted to 9 neurovascular care centers, the incidence of stroke was 1.3% (88/6698), and of these, 60% were LVOs.[1] Similarly, the acute LVOs of the 12 centres were analyzed and a total of 66 patients were identified, whose mean age was 51 yr, and of whom 42 underwent treatment with mechanical thrombectomy. This suggests that stroke is a neurological complication of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, whose pathophysiology may be explained by the state of generalized hypercoagulability and endothelial dysfunction caused by this virus.[1,2] A plethora of scientific literature has been published in the last few months exploring stroke and several links, including mast cells, histiocytes, thrombotic complications, and, but not limited to, neuroinflammation in neurological complications of COVID-19.

As with most of the clinical data on COVID-19, the scientific community recognized neurological complications as a recognized marker of severe COVID-19 with a call for action to prevent significant morbidity and mortality.[3,4] We thank Khandelwal et al[1] for providing such valuable evidence; however, we would like to make a few comments. COVID-19 resulting in LVO and stroke in the young population has been predominantly reported as case reports and small series.[5,6] In the present study by Khandelwal et al,[1] 16% had LVO under 50 yr of age. This further suggests the validity of existing pathogenic mechanisms of COVID-19 resulting in LVO as stroke in the young population. The authors have included patients with acute ischemic stroke (AIS) with COVID-19 in this study. The findings need to be interpreted with caution as the authors have not mentioned how many of these patients had COVID-19 following the development of AIS and how many had an AIS following the development of COVID-19. Since AIS has been described as a comorbidity with increased risk of adverse events for COVID-19 and vice versa,[3,7,8] it is essential to identify COVID-19 patients complicated by the development of AIS and AIS patients complicated by COVID-19. It has been shown that, during the acute phase of infection, approximately 36% of cases develop neurological symptoms such as dizziness, headache, altered consciousness, and seizures.[2,9] In mild to moderate cases, patients report anosmia (85.6%) and taste alterations (88%), while the development of ischemic stroke may be related to the severity of the disease or preexisting vascular risk factors, manifesting itself with classic neurological signs (hemiparesis, aphasia, and dysarthria, among others).[2,9] Also, specific subacute neurological disorders have been reported to develop within 3 to 10 d after the development of respiratory symptoms, including Guillain-Barré syndrome and Miller-Fisher syndrome.[2,10]

The primary mechanism by which these manifestations occur is through neuroinflammation, which is mediated by increased activity of proinflammatory immune pathways that negatively impact brain homeostasis and function, including blood-brain barrier dysfunction leading to infiltration of inflammatory cells into the central nervous system.[2,9] This event contrasts with the results obtained in the study by Khandelwal et al,[1] where they report that patients with LOV had increased levels of C-reactive protein and D-dimer, which are serological markers of inflammation. The role played by the NLR Family Pyrin Domain Containing 3 (NLRP3) inflammasome in the acute and probably chronic phase in neurological disorders caused by COVID-19 has also been reported.[2] The latter affects the immune functions of the brain, thereby causing pathological accumulation of neurodegeneration-associated peptides, such as fibrillar amyloid-β, inducing or exacerbating neurodegenerative processes.[2] Likewise, experimental studies have shown that ventilation-induced hypercapnia induces cognitive impairment in an NLRP3 inflammasome-interleukin-1β-dependent manner.[2]

Based on the above, it can be estimated that there is a relationship between SARS-CoV-2 infection and the occurrence of neurodegenerative diseases and neurological disorders mediated by inflammation, mainly Alzheimer's disease.[2,9] Therefore, it is likely that a percentage of individuals who recovered from the infection will experience neurological and cognitive impairment in later years. Further studies are needed to explain and answer the questions arising from this interaction. Post-COVID-19 Neurological Syndrome (PCNS) is another important clinical condition to consider, which encompasses several symptoms and neurological effects related to infection after the acute phase of the disease.[11] It has been observed that, even in patients with mild symptoms, symptoms such as dizziness, muscle weakness and pain, fatigue, headache, and anosmia persisted for months.[11] Also, mental illness such as depression, post-traumatic stress disorder, and anxiety are psychiatric disorders that can also occur weeks after infection and are related to psychological factors or neurobiological lesions.[12,13]

In this order of ideas, the immune and inflammatory mediators of the specific pathophysiology associated with SARS-CoV-2 infection determine the mechanisms by which acute or chronic

neurological symptoms appear. Thus, we consider that COVID-19-positive patients with ischemic stroke are more likely to suffer from the aforementioned neuropsychiatric disorders and much more severe PCNS, as well as an increased likelihood of neurodegenerative diseases in individuals with or without predisposing genetic factors, all as a result of neuroinflammation as a common causal factor of these manifestations. Finally, it is important to highlight the importance of continuous neurological, cognitive, and affective follow-up of surviving patients, due to the neuroinvasive potential and neurological sequelae resulting from the infection. It is therefore essential that neurologists and psychiatrists are prepared for an increase in the incidence of patients with this type of disease in the coming years.

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