SARS-CoV-2 as a Potential Trigger of Neurodegenerative Diseases

We read with great interest the article from Lippi and colleagues[1] about the potential role of severe acute respiratory syndrome *coronavirus* 2 (SARS-CoV-2) in the future development of neurodegenerative diseases and specifically Parkinson's disease.[1] We found the article interesting because the potential mechanisms through which SARS-CoV-2 could trigger degeneration in invaded central nervous system cells are reviewed. The authors propose different mechanisms associated with aging and the molecular changes that could promote the development of Parkinson's disease and other neurodegenerative disorders in the future. We would like to contribute with some aspects that may support the hypothesis of the authors.

The presence of other coronaviruses in the central nervous system has been previously described in the elderly in cases of Alzheimer's disease, Parkinson's disease, and multiple sclerosis.[2] Thus, this hypothesis is also possible with Coronavirus Disease-2019 (COVID-19). In this regard, recent pathological findings of patients with COVID-19 have found SARS-CoV-2 in brain tissue. We reviewed the neuropathological findings of cases reported until now, which are summarized in Table 1. In 2 cases, intracytoplasmatic SARS-CoV-2 was found.[3,4] Inter-

TABLE 1 COVID-19 autopsies with neuropathological analysis

			Microscopic Analysis						
						Electron Microscopy			
Reference	Anatomical Areas	Macroscopic Analysis	Histology (Hematoxylin and Eosin Stain)	Gliosis	Microgliosis	Intracellular Virus	Cytoplasmic Vacuoles	Inclusions	Inflammatory Signs
Liu et al[5]	ND; external macroscopic study	Cerebral atrophy and stroke	ND	ND	ND	ND	ND	ND	ND
Ding et al[6]	ND; external macroscopic study	Neurodegeneration	ND	ND	ND	ND	ND	ND	ND
Paniz-Mondolfi et al[3]	Frontal lobe brain	ND	ND	ND	ND	Yes	Yes	Yes	No
Wichmann et al[7]	ND; external macroscopic study	2/12 patients; cerebral sclerosis only macroscopic analysis	ND	ND	ND	ND	ND	ND	ND
Menter[8]	ND	Analysis of the brain revealed 3 of 4 brains examined showed mild hypoxic injury	Yes; no evidence of inflammatory infiltrates or neuronal necrosis.	No	No	ND	ND	ND	N
Bulfamante et al[4]	Olfactory nerve, gyrus rectus, brainstem (medulla oblongata)	ND	Widespread tissue damage involving the neurons, glia, nerve axons, and myelin sheath	ND	ND	Yes	Yes	No	No

The anatomopathological parameters used in the histological analysis are shown in the supplementary material.
COVID-19, Coronavirus Disease-2019; ND, not determined or not described.

*Correspondence to: Ulises Gomez-Pinedo, Institute of Neurosciences, San Carlos Health Research Institute, Universidad Complutense, Profesor Martin Lagos s/n. 28040, Madrid, Spain; E-mail: u.gomez.pinedo@gmail.com

Relevant conflicts of interests/financial disclosures: Nothing to report.

Received: 19 May 2020; **Accepted:** 21 May 2020

Published online in Wiley Online Library (wileyonlinelibrary.com). DOI: 10.1002/mds.28179

estingly, none of the 5 pathological cases reported gliosis, microgliosis, or markers of inflammation, including those in which the virus was detected. In these cases, the virus was observed inside vacuoles and/or inclusions. This type of vacuolation might suggest that the structures that are present in neurodegenerative diseases to include unfolded proteins.

Although the central nervous system is not one of the organs with the highest expression of Angiotensin-Converting Enzyme-2 receptors (ACE2), their cells also have these receptors as well as the expression of Transmembrane Serine Protease 2 (TMPRSS2). Intriguingly, the cortex and the substantia nigra are brain regions with high expression and thus they have higher possibilities of penetration of the virus by ACE2. In addition, both regions are associated with the most frequent neurodegenerative diseases.

Large virion-containing vacuoles were described in previous studies with Middle East Respiratory Syndrome coronavirus (MERS-CoV) and Severe Acute Respiratory Syndrome coronavirus (SARS-CoV).[9] For this reason, SARS-CoV-2 vacuolization should not be unexpected. However, in our opinion, one of the most striking findings in the brain tissue images reported with COVID-19 is the absence of inflammatory signs. This could suggest that vacuolization may be a defense against the infection, but not a response as in other viral encephalitis. This mechanism would support the authors' approach about the role of this virus in neurodegeneration. However, further research and more pathological cases with brain examination are necessary to clarify this issue.

Ulises Gomez-Pinedo,* Jorge Matias-Guiu, Inmaculada Sanclemente-Alaman, Lidia Moreno-Jimenez, Paloma Montero-Escribano and Jordi A. Matias-Guiu

Department of Neurology, Laboratory of Neurobiology, Institute of Neurosciences, Health Research Institute of the Hospital Clínico San Carlos, San Carlos Clinical Hospital, Universidad Complutense, Madrid, Spain

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Supporting Data

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