Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Letter to the Editor

Neurotropism of SARS-CoV 2: Mechanisms and manifestations

Dear Editor,

SARS-Cov-2 is a beta-coronavirus that shares similarities with SARS-CoV. So far, it is proposed that it binds by glycoproteins expressed on its surface to the receptor of the angiotensin-converting enzyme 2, which is distributed in the respiratory tract epithelium, the lung parenchyma and other areas such as the gastrointestinal tract, endothelial cells, among others [1].

Respiratory involvement is the most common in patients confirmed with Covid-19, however there are already reports of neurological manifestations [2,3]. It should be mencioned that the central nervous system (CNS) involvement was also reported in other coronaviruses [4] and studies in humans and experimental models revealed a possible neural pathway given by the olfactory nerve [5–7].

Viruses can reach the CNS through hematogenous or neural propagation [8]. Nerve dissemination is possible by the polarization of neurons, this property gives them the ability to receive and transfer information. This transport can be retrograde or antegrade and is facilitated by proteins called dinein and kinesin, which can be targets of viruses [9]. Once entered the CNS, viruses can generate alterations in neurons, as evidenced by a study carried out by Gu et al., who detected in 8 autopsies of victims of SARS, neuronal histopathological changes in the cortex and hypothalamus [6].

The olfactory pathway begins in bipolar cells located in the olfactory epithelium, from there its axons and dendrites extend to the olfactory bulb, where they make synapses with the cells present in this structure. Subsequently, this cranial pair is divided into two branches and is directed towards the olfactory nucleus present in the pyriform cortex [10] . This nerve route has been used by some coronaviruses in rodent models exposed to nasal inoculation [11,12]. For example, after exposure to SARS-CoV by inhalation, Netland et al. detected the coronavirus after 60 h in the olfactory bulb and after four days its dissemination to the pyriform cortex and dorsal nucleus of the rafe was confirmed, the latter located on the brain stem [11]. Similar results were found in a Canadian study with another coronavirus, HCoV-OC43. In this case, by the fourth day of inoculation, the virus had already spread to the piriformis cortex, brain stem, and spinal cord [12]. On the other hand, a study from the 1990s showed that interruption by ablation in the olfactory pathway did not allow the neural spread of the MHV coronavirus in an animal model [7].

The interesting thing about this possible propagation mechanism is the presence of the virus in areas of the brain stem [11,12], because this structure contains nuclei that regulate the respiratory rhythm. Breathing has central control given by the regulation of a number of neural groups. Through the nucleus of the solitary fascicle, the CNS receives information from the chemoreceptors that detect changes in the concentrations of CO2 and O2, alterations in these components lead to an increase or decrease in respiratory effort [13]. In this way, stem nuclei have connections with the respiratory system [1,13], and the entry of the coronavirus into this structure could trigger death by alteration of these neuronal groups [1].

In January 2020, Chen et al. published a retrospective analysis based on 99 patients diagnosed with SARS-COV-2 pneumonia at a hospital in Wuhan, China. In order to describe the epidemiological, demographic, clinical and radiological characteristics of these patients. The neurological symptoms presented were confusion and headache in 9% and 8%, respectively [14].

Months later, Mao et al. published a retrospective case series at 3 hospital centers in Wuhan, China. This included 214 patients with a molecular diagnosis of SARS-CoV-2 acute respiratory distress syndrome. The presence of neurological symptoms was evaluated in 3 categories: central, peripheral and musculoskeletal symptoms. In their analysis they found that 36.4% of the patients had neurological symptoms, these being directly related to the severity of the patient (severe cases VS non-severe: 40 [45.5%] vs. 38 [30.2%], $P < .05$). In patients with central symptoms (24.8%), 16.8% and 13.1% presented dizziness and headache, respectively. Among the peripheral symptoms (8.9%), the most common were hypogeusia and hyposmia with 5.6 and 5.1%. On the other hand, significant differences were found when comparing the presence of stroke (5 [5.7%] vs. 1 [0.8%], $P < .05$), alteration of the state of consciousness, severity (13 [14.8%] vs 3 [2.4%], $P < .001$) and muscle damage (17 [19.3%] vs 6 [4.8%], $P < .001$), according to the level of severity of the cases [3].

In addition to this, case reports have shown neurological alterations in patients with COVID-19, so far, we have found 4 cases; one is that of a 79-year-old patient, who enters with altered state of consciousness and a febrile history associated with coughs of several days of evolution. Imaging and laboratory studies showed massive intracerebral bleeding from the right hemisphere and RT - PCR positive for SARS-CoV-2, this event can be explained by the presence of receptors of the angiotensin-converting enzyme 2 in the cerebral vascular endothelium and its self-regulatory function that when invaded by the virus reduces its functionality causing elevation of cerebral blood pressure and as a consequence, the blood vessel rupture [15].

On the other hand, Filatov et al. report a case of an older adult patient with multiple cardiovascular and pulmonary pathological antecedents, in addition to Parkinson's disease, which consults the emergency department due to increased respiratory distress, persistence of fever, headache and altered mental status. Cranial tomography without acute alterations, electroencephalogram with findings of focal dysfunction of the left temporal lobe and focus of epileptogenicity, study of the cerebrospinal fluid (CSF) reported within normal limits, without detection of the virus. Based on these findings, it was considered that in addition to respiratory symptoms, the patient had encephalopathy [2]. In contrast, Zhou et al., detected the presence of the virus genome in the CSF of a 59-year-old patient with COVID-19 pneumonia, diagnosing viral encephalitis, demonstrating the direct damage that the virus produces in the CNS [16].Finally, Poyiadji et al.,

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report the case of a patient with acute necrotizing encephalopathy diagnosed by images, associated with COVID-19, probably related to the cytokine storm that it produces within the CNS [17].

The aforementioned makes us think that respiratory distress is not only the result of pulmonary inflammatory structural damage, but also due to the damage caused by the virus in the respiratory centers of the brain, making it more difficult to manage these patients.

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