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COVID-19: what if the brain had a role in causing the deaths?

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In the last few weeks Italy first, and then several other countries across the world, have been swept up by the deadly wave of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which causes the illness named COVID-19, from the acronym CO (corona) VI (virus) D (disease) and 19 (year of the virus identification). The medical community is working day and night to

assist affected people and experts in communicable diseases are striving in multiple ways to understand the progression of events leading to the lethal respiratory syndrome.

Lombardy is the most heavily affected area in the Italian coronavirus epidemic and the one with the highest number of reported fatalities. Doctors assisting patients in the front-line of the Policlinico San Matteo of Pavia, one of the Italian hospitals with the highest number of SARS-CoV-2 cases, report that several patients in the latest stages of disease, when their lung parenchyma is devastated by the infection, may not manifest dyspnea (personal observations). Data from the Wuhan area show that more than 90% of patients in need of intensive care cannot breath spontaneously (Wang et al., 2020). On the other hand, patients with severely affected lungs may be paucisymptomatic and recover fully from the infection.

Thus, at least in some cases, there seems to be a discrepancy between the severity of the lung involvement and the respiratory function. Severe Covid-19 leads to death via multiple mechanisms, including myocardial injury, kidney failure, shock, disseminated intravasal coagulopathy (Guo et al., 2020; Wang et al. 2020). However, an additional explanation worth exploring in this phase of uncertainties, also in the light of the initial evidence of neuronal localization of COVID-19, is that the respiratory failure may be driven by a dysfunction of the cardiorespiratory centers in the brainstem.

Coronaviruses (CoVs) are neurotropic (Li et al., 2004) and SARS - CoV particles have been detected in neurons of human brain (Ding et al., 2004; Gu et al., 2005). Given the high level of genetic homology of CoVs, which also share many other characteristics, it is also likely that SARS-CoV-2 may gain access to the central nervous system (CNS), where it can induce neuronal injury. The peripheral invasion of nerves by SARS-CoV-2is further suggested by the occurrence of anosmia and ageusia in more than 5% of a population of 214 COVID-19 people (Vaira et al., 2020). From the peripheral nerves the virus may have access to the central nervous system via trans-synaptic transfer, a possibility documented for other coronaviruses in vitro and in vivo (Mengeling et al., 1972). Recent experimental evidence demonstrates that a human CoV strain, HCoV OC43, can travel from the nasal cavity to the olfactory bulb, then spreading to the piriform cortex and ultimately to the brainstem, via both passive diffusion and axonal transport (Deforges et al., 2019; Dube et al., 2018). Alternatively, or in addition – which would increase CNS

vulnerability to SARS-CoV2 diffusion - the virus may travel retrogradely along the vagus nerve, which innervates many of the visceral organs that can be invaded by the virus beyond the lungs, such as the heart and the gastrointestinal tract. Once in the vagal nerve endings, retrograde axonal transport may grant access to the brainstem.

Whatever the entry point, the final destination of SARS-CoV2 could be the neurons of the nucleus of solitary tract in the medulla oblongata, which form the dorsal respiratory group that generates the basic rhythm of respiration and emits repetitive bursts of inspiratory neuronal action potentials. The nucleus of the solitary tract is connected with the nucleus ambiguus, the main components of the ventral respiratory group that controls forceful inspiration and expiration. Interestingly a similar efferent pathway can also be traced for the cardiac control centre.

A recent restrospective analysis of COVID-19 manifestations in 214 subjects in the Wuhan area reported the presence of neurological symptoms in 36% of them, a percentage that rises to 44% when considering the most severely affected subjects. Thus, it is possible that the invasion of the nervous system by SARS-CoV-2is one of the pathogenetic mechanisms leading to death. This is a call to action for using the available sophisticated neuroimaging, neurophysiological and biochemical techniques to detect and document SARS-CoV-2 invasion of the peripheral and central nervous system. These investigations will of course greatly benefit also from systematic histopathological analyses of autoptic tissues to enhance our understanding of the preferential routes of invasion and sites of possible neuronal damage. This may clarify additional modalities through which Cov-2 is killing people all over the world, possibly provide markers for the identification of the subjects who are at higher risk to evolve in the more serious manifestations of COVID-19 and, even more importantly, foster the identification of additional therapeutic strategies.

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