Opinion Piece

Neuropathologists play a key role in establishing the extent of COVID-19 in human patients

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Abstract

SARS-CoV2 infection causes COVID-19, and represents the most emergent health care crisis of our generation. Ample evidence in the scientific literature suggests that SARS-CoV, MERS-CoV, and endemic human coronaviruses infect brain cells. We delineate a rationale for encouraging evaluation of the brain, and in particular the brainstem, in COVID-19 so that potential neuropathological mechanisms can be delineated.

Keywords: COVID-19, SARS-CoV2

SARS-CoV2 infection causes COVID-19, and represents the most emergent health care crisis of our generation. SARS-CoV2 is a member of the betacoronavirus family that includes the severe acute respiratory syndrome CoV (SARS-CoV) and Middle East respiratory syndrome CoV (MERS-CoV), both of which have caused fatal infections in the past two decades (Huang et al., 2020). Although most people recover from the disease, SARS-CoV2 can cause severe respiratory distress syndrome, particularly in older patients and patients with underlying comorbidities (Mahase, 2020). Most of the patients who require intensive care ultimately become unable to breathe spontaneously (Wang et al., 2020). Although SARS-CoV2 shows its effects predominantly on the respiratory system, the primary pathophysiology behind the respiratory dysfunction and mortality remains elusive. Previous findings of SARS-CoV infection and other coronaviruses in the nervous system bring to mind the possibility that SARS-CoV2 infection can cause respiratory failure by disrupting the cardiorespiratory center in the brainstem and are briefly reviewed below.

It is known that most coronaviruses share similar viral structures and infection pathways (Baig et al., 2020). These structural and pathophysiological similarities between other coronaviruses and SARS-CoV2 likely indicate that pathophysiological insights from other coronavirus studies may be generalizable to SARS-CoV2. SARS-CoV and SARS-CoV2 have high protein homology (Baig et al., 2020), and SARS-CoV2 uses the same receptor to enter the host cells with at least 10 times higher affinity relative to SARS-CoV (Wrapp et al., 2020). Although multiple candidate receptors have been proposed, cellular infection through interaction with the Angiotensin (Ang) converting enzyme (ACE2), a transmembrane carboxypeptidates sharing homology to ACE1's extracellular domain but with unique transmembrane and intracellular domains (Riordan, 2003), seems to be critical in the pathogenesis in SARS-CoV (Baig et al., 2020). Although ACE2 is capable of modifying angiotensin I, it catalyzes angiotensin I to Ang- (1-9) rather than to Ang II, and plays diverse physiological roles (reviewed by (Clarke and Turner, 2012)). ACE2 is expressed in air-

way epithelia, lung parenchyma, vascular endothelia, kidney cells, small intestine cells (Li et al., 2020) and also in the brain, particularly in glial cells and neurons (Baig et al., 2020). We also note that endemic human CoVs have neuroinvasive potential (Desforges et al., 2014). With this in mind, several studies have explored the extent to which zoonotically transmitted CoVs affect human brain function. Studies using different mouse lines transgenic for the expression of ACE2 showed extensive virus replication in the brain, likely mediated through retrograde transport through the olfactory bulb. Among the brain regions affected by the virus, thalamus, cerebrum and brainstem were severely impacted. While in the K18-hACE2 transgenic line, the SARS-CoV infection induces neuronal death as a result directly from the neuronal and not pulmonary infection. An abundant neuronal loss was found along with increased inflammatory cytokines, and proliferation of microglia, but not of astrocytes (McCray et al., 2007; Netland et al., 2008). Additional Studies using transgenic mice demonstrated enhanced levels of IL-6, IL-12p40, G-CSF, CXCL1, MIP-a and MCP-1 in brain homogenates 3 days after the infection resulting in an inflammatory cytokine reaction (Tseng et al., 2007). Such cytokine elevations and extensive neuronal pathologies in the brainstem were also noted in MERS-CoV infections (Li et al., 2016). In this same study, the authors showed evidence of viral replication in primary and porcine astrocytes and human glioblastoma and neuroblastoma cell lines (Li et al., 2016). It is not well established how SARS-CoV infection affects astrocytes *in vivo* and how it mediates the neuronal damage of this syndrome, despite the fact that ACE2 is expressed in isolated astrocytes from brainstem, cerebellum and medulla (Gallagher et al., 2006; Gowrisankar and Clark, 2016). On the other hand, expression of ACE2 at mRNA and protein levels in neurons is also documented. *In vivo* findings have shown ACE2 expression in neurons of the paraventricular nucleus (PVN), area postrema (AP), dorsal motor nucleus of the vagus (DMNV), nucleus of tractus solitarii (NTS), the rostroventrolateral medulla (RVLM), and the nucleus ambiguous (NA), all brain structures related to cardiovascular and respiratory function (Doobay et al., 2007). Furthermore, we do not know the extent to which SARS-CoV affects brains of newborn babies. For instance, a timely study emerging from China performed on COVID-19 outcomes on pediatric patients demonstrated that the severity of COVID-19 in children less than 1-year-old was very high (53.8% showing critical course) relative to other age groups (Dong et al., 2020). Neurological manifestations of COVID-19 have also been documented. In a preprint study from China, one of 3 patients suffering from SARS-CoV2 had neurological manifestations, including dizziness, headache, impaired consciousness, hypogeusia (reduced ability to taste) and hyposmia (reduced ability to smell) (Mao et al., 2020), the latter symptoms suggesting neuronal involvement of areas in proximity to the olfactory bulb. Another possibility of trans-synaptic transfer of SARS-CoV2 is the usage of neuroanatomic interconnections of the respiratory and gastrointestinal system to nuclei of the brainstem as has been noted by the avian influenza virus (Li et al., 2020). Finally, SARS-CoV2 could disseminate through the blood to the brain via crossing endothelial cells that express the ACE2 receptor as another way of transfer (Baig et al., 2020).

In conclusion, there is growing evidence that the brain could be the main trigger in the severity of COVID-19, but there is a paucity of evidence derived from human patients. According to the interim guidance of the American Centers for Disease Control (CDC) in March 2020, CDC recommends collecting swab specimens, samples for postmortem microbiologic and infectious disease testing, formalin-fixed autopsy tissues from lung, upper airway, and other major organs, if an autopsy is performed for a confirmed COVID-19 case (Center of Disease Control and Prevention, 2020, March 25). However, additional concerns have also been raised regarding the use of oscillating saws, a tool commonly used during brain procurement, as these saws have been shown to promote aerosolization. Nevertheless, we believe that documenting the extent of CNS involvement in severe manifestations, including documenting which brainstem nuclei may be affected in the autopsies is crucial to clarify the pathophysiology of COVID-19. We also recognize that in areas ravaged by the scale of infection and COVID-19 disease, investment in personal protective equipment for autopsy would represent an unwise decision when front-line workers remain unprotected. We therefore suggest that a coordinated effort between health systems work together to meet this goal. Drawing inspiration from the neuropathological evaluations of brains of HIV infected patients (Petito et al., 2003), we suggest that a study design composed of 20 brains procured from COVID-19 infected decedents be performed, with extensive sampling of brainstem nuclei to include structures implicated in human control of respiration, including the locus coeruleus (Nobuta et al., 2015), ventral medulla (Rudzinski and Kapur, 2010), and preBotzinger complex (Schwarzacher et al., 2011). It would also be important to evaluate COVID19 infected decedents without significant neurological manifestations as potential controls. In this way, highly impactful descriptive studies of COVID-19 disease can be achieved and the burden of investing in personal protective equipment can be shared by various centers.

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