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Mini Review

Does COVID-19 Affect White Matter?

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Abstract

Herein, the extremely scant literature evidence for whether COVID-19 affects central nervous system (CNS) white matter is reviewed, largely through clinical case studies. Because of its relative novelty, there is very little in the literature by way of basic research on how the virus interferes with nerve transmission, one of the principle functions of white matter. Further, there is a call that causes of death are not attributed to COVID-19 infection, just because the patient tests positive for the virus at the time of death, especially when other medical problems are present.

Keywords: *COVID-19; Coronavirus; CNS; Brain; White Matter; Oligodendrocytes*

Introduction

Although as of this writing, it has been a mere eight months since the beginning of the global pandemic, the literature is already replete with studies, focused on characterizing the molecular and cellular mechanisms of COVID-19 infection. Much of what is known about this virus has been aided by studies of some of its predecessors, such as those of the family of viruses, comprising the coronavirus (e.g. SARS-CoV-2). Although the literature on the effects of COVID-19 on various organ systems [1] has burgeoned over the last six months, studies have not been systematic; indeed, much of our knowledge comes from clinical case studies, which are, of course, at the mercy of patient consent and availability [2]. And even though several excellent reviews in both scope and depth, addressing the neurological and cellular pathways, reactions and mechanisms have recently been published (see below), it is still not known which parts of the brain are most susceptible, as well as which kinds of neurons and glia cells are most vulnerable to becoming infected. Specifically, for example, how is white matter affected? Of course, the short answer would be: "It's too early to tell for sure".

The preferred route of entry and the events that follow

Such white matter involvement would affect glia cells either directly infecting them or indirectly, by infecting neurons, eventually dissipating the latters' resting membrane potentials, possible hyperactivity ensues, and, if all goes well, apoptosis; if all does not go well, then necrosis. Either way, the resultant neuronal loss would result in greatly impaired cognitive and memory function as well as eventual mood destabilization, leading to (severe) psychological disturbances, the severity all of which, would depend on the brain region(s) in which these are occurring. Entry of COVID-19 into the brain unleashes a massive barrage of cytokines, colloquially now known as the "cytokine storm", which results in a massive toxic neuroinflammatory cascade [1,3-11], which will be set into motion once COVID-19 is in the brain; therein, neurons and glia are both susceptible because they express ACE2 receptors, which the virus uses to enter the cells [1,7,12,13].

Much neurological dysfunction leading to CNS-based impairments, such as stroke, spinal cord injuries and headaches [14] could make the patient more susceptible to COVID-19 infection, but there is no conclusive evidence that the virus creates these problems from scratch, on its own, with the possible exception of loss of taste [15] and smell (anosmia [15,16]), since there is considerable evidence that the virus enters the CNS (primarily) through the nose [4,6,8,12,14,17-19], besides through other routes, such as from the peripheral circula-

tion by hijacking blood cells or by causing meningeal inflammation, leading to a compromised blood-brain barrier [4,8,11]. Alternatively, the virus can gain entry into the CNS from any of the eight circumventricular sites known not to have a blood-brain barrier: pineal gland, subcommissural organ, choroid plexus, area postrema, neurohypophysis, median eminence, vascular organ of the lamina terminalis and the subfornical organ.

Clinical evidence

Consistent with findings that only a little more than a third of COVID-19-infected patients present with neurological symptoms (34.6% [8]), much of the clinical evidence comes from clinical single-case [19-21] or small-sample size [22-24] studies, in which the patients present with other neurological problems [9,10,19,25], such as encephalomyelitis [22,26,27], encephalitis [27], encephalopathy [13,16,28], stroke [16,27,28], headache and vertigo [7], meningoencephalitis [16], convulsions and cerebrovascular disease [13,16] or Guillain-Barré Syndrome [27] and cognitive, memory [29] and confusion, suggesting hippocampal vulnerability to the virus, as well as psychological problems [10,23,30], such as depression, possibly triggered by anosmia [15], were co-morbid with COVID-19 infection [25]. Only on a case-by-case basis, taking medical history into account, can physicians determine how large a role the virus has played in the etiology of these co-morbid problems. Thus, it is not known overall whether the virus is directly (or indirectly) responsible for these other neurological problems [27]. One very possible direct cause of death would be by compromising the brainstem respiratory centers [18].

White matter involvement

Considering the foregoing clinical evidence, it is difficult to imagine that white matter would not be involved. Indeed, many of these problems are the demyelinating results of viral infection [10,16,22]. However, there is surprisingly little evidence, from both a basic science and clinical perspective, with regard to the virus' effects on white matter per se. As indicated above, the neuropathological sequelae of COVID-19 infection of CNS neurons would certainly involve white matter; but clinically, the evidence is far from conclusive, as much of these findings are the result of clinical case studies. For example, in a COVID-19-infected patient, the globus pallidum white matter and corpus callosum [20,28,31], internal capsule [5] and periventricular region [21] had lesions. In addition, white matter microhemorrhages [23,24,31,33] were particularly profuse throughout the cerebral cortices [32] and basal ganglia [28]. Such microhemorrhages could be the result of a compromised blood-brain barrier, overwhelming the structural integrity of astrocytic connectivity with the microvasculature. This could be achieved because endothelial cells are known to express the angiotensin-converting enzyme 2 receptors to which COVID-19 binds [34], thereby increasing the perivascular space and compromising the blood brain barrier. In addition, oligodendrocytes and neurons themselves may be infected by the virus, thereby directly disrupting white matter and the axons that had been serving as their structural supports, respectively. Such infections may lead to secondary effects, such as inflammation. Consistent with the above-mentioned evidence of encephalomyelitis [22,26,27], inflammation has been observed to occur following coronavirus infection - induced chronic demyelinating encephalomyelitis in which the amount of demyelination was associated with the numbers of T-cells, microglia and macrophages, depending on the CNS region [35]. Such demyelination could be the result of an increased immune response and lead to the formation of antibodies against various proteins that contribute to myelin, such as myelin oligodendrocyte glycoproteins in COVID-19-infected patients in the deep subcortical white matter regions in the temporal and occipital lobes [36] and retina-optic nerve [37]. Moreover, in patients with spinal cord injury, there are many other CNS-related problems, such as depression and stress, immunosuppression, hypertension and if the injury is higher than T8, possible respiratory failure, all of which can be exacerbated by COVID-19 infection [38].

Conclusion

One of the current controversies is how COVID-19-related deaths are actually counted. If a patient was already medically compromised, say, for example, with a T5 spinal cord injury, and he also tested positive for the virus, and then died, what is recorded as the official

cause of death? Although it is possible that the viral infection exacerbated the spinal cord injury from the point of view of compromised brainstem respiratory function, it is important for clinicians to be treat every case uniquely, since no two cases would be identical, rather than just to assign viral infection as the cause of the death, just because the patient tested positive. Such a practice would obviously inflate the true number of COVID-19-caused deaths.

Herein I have highlighted that the pathophysiology of what has been clinically observed will be more thoroughly characterized with more basic cellular and molecular research of how coronavirus interferes with nerve transmission.

Conflict of Interest

The author declares that no conflict of interest exists.

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