



Mini Review

Delirium in Severe Acute Respiratory Syndrome-Coronavirus-2 Infection: A Point of View

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Abstract

Coronavirus disease 2019 was for the first time reported in December 2019 in China, and has since spread throughout the world as a pandemic. In this point of view, we aim to discuss the occurrence of central nervous system symptomatology, and delirium, in patients suffering coronavirus disease 2019. To date, most of the research done around this infectious disease caused by severe acute respiratory syndrome coronavirus 2 have focused on its general manifestations (fever, cough, fatigue, and/or shortness of breath) and the different aspects of its pathogenesis regarding the respiratory system. While less articles have focused on the neurocognitive alterations produced by severe acute respiratory syndrome coronavirus 2 infection, only a few have focused on delirium as severe acute respiratory syndrome coronavirus 2-infection-based central nervous system manifestation. Nonetheless, emerging evidence shows that coronavirus disease 2019 could seriously affect the central nervous system. Since the current outbreak of coronavirus disease 2019 continues to constitute a public health emergency of international concern, here, we review the existing evidence on the mechanism of severe acute respiratory syndrome coronavirus 2 infection leading to central nervous system manifestations in general, delirium in particular, finally discussing the existing interaction between severe acute respiratory syndrome coronavirus 2 and Angiotensin-Converting Enzyme-2 receptors in the brain, a possible pathogenic process leading to the delirium symptomatology observed in some of the patients suffering the disease.

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Background

The already declared by the World Health Organization Coronavirus disease 2019 (COVID-19) pandemic [1], provoked by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [2], and initially identified and recorded in December 2019 in Wuhan, capital of Hubei Province, China, is already considered the global health crisis of our time, and constitutes the greatest challenge we have ever faced since World War Two, with profound and severe social and economic consequences.

As of 25 August 2020, COVID-19 confirmed global cases exceed 23.5 million, while confirmed global deaths exceed 811000 over 188 countries and regions. In this respect, America, Asia and Europe are the worst-affected continents, with the United States of America (5738056 confirmed cases and 177229 reported deaths), Brazil (3622861 confirmed cases and 115309 reported deaths), Mexico (560164 confirmed cases and 60480 reported deaths), India (3106348 confirmed cases and 57542 reported deaths) or the United Kingdom (328617 confirmed cases and 41519 reported deaths) particularly hard hit [3].

The novel COVID-19 is the seventh known coronavirus infecting humans [4]. After less than a week of infection, the most characteristic symptoms of patients suffering COVID-19 include fever, cough, fatigue, or shortness of breath [2]. Nonetheless, although SARS-CoV-2 mainly targets and infects the lungs, the damage it provokes can extend to other major organs, including the brain. Indeed, emerging data is signalling that some COVID-19 patients also show atypical Central Nervous System (CNS) manifestations such as headache, loss of taste and smell and, interestingly, delirium. In this regard, recent studies from China, France or the United Kingdom have identified the presence of neurological symptoms in COVID-19 patients. Neurologic signs were recorded in France in 84% patients (N=58) suffering severe COVID-19 on ICU admission and before treatment, including patients presenting delirium features such as inattention, disorganized thinking and altered level of consciousness (44%) [5]. In 3 centres in Wuhan, China, 36.4% of hospitalized patients (N=214) diagnosed with COVID-19 commonly showed neurologic manifestations, especially when they were suffering the more severe forms of the disease, including impaired consciousness (14.8%) [6]. In a recent UK-wide surveillance study, neurological and neuropsychiatric complications were recorded in patients that developed COVID-19, with 39 (31%) of 125 patients presenting altered mental status, comprising 10 patients with neuropsychiatric disorders presenting new-onset psychosis [7]. As a result, is especially important to understand delirium in the specific context of COVID-19, since delirium is a frequent manifestation of infection, it may be regarded as an early infection symptom, and there is concern that long term cognitive consequences in patients suffering COVID-19 may emerge.

Although the primary target of coronaviruses (CoVs) is the respiratory epithelium, and they are not generally neurotropic virus, how is SARS-CoV-2 infection contributing to the pathophysiology of delirium?

Delirium

Delirium, a serious disturbance in mental abilities, encompasses an organic-based decline from a preceding baseline mental status, develops over a short period of time, and includes disturbances in cognition, attention, consciousness, and perceptual disturbances (such as delusions and/or hallucinations) [8]. As a confusional state, delirium is caused by an acute biological process at the structural, functional, and/or chemical level in the brain and, importantly, it may arise from an existing disease process outside the brain (e.g. SARS-CoV-2 infection) or any acute predisposing factor that, organically, affect the brain at the neurotransmitter, neuroendocrine, and/or neuro inflammatory level in an already vulnerable brain [9].

Mechanism of SARS-CoV-2 Infection Leading to Delirium

New and emerging evidence suggest that delirium onset and/or development in the context of SARS-CoV-2 infection is possibly due to multiple factors, including (1) hypoxia and oxygen deficiency of the brain, (2) neuronal inflammation due to cytokine storm as a result of a strong activation of the immune system, and/or (3) direct CNS invasion and neuronal toxicity [10].

Hypoxia, a condition in which the body and/or a region of the body, such as the brain, is deprived of oxygen at the tissue level, can result in neuronal swelling and brain edema which can lead to neurological and brain damages [11]. For instance, microscopic examination of brain specimens obtained from 18 patients who died 0 to 32 days after the onset of symptoms of Covid-19 showed acute hypoxic injury in the cerebrum and cerebellum in all the patients, with loss of neurons in the cerebral cortex, hippocampus, and cerebellar Purkinje cell layer [12]. Brain immune mediated injury, on the other hand, is due to the cytokine storms, a fact that increases the levels of inflammatory cytokines and activation of T lymphocytes, macrophages, and endothelial cells, causing a release of Interleukins 6 (IL6), vascular leakage, activation of complement and coagulation cascade, and disseminated intravascular coagulation, finally producing brain damage [13].

Finally, and although direct CNS invasion and neuronal toxicity is not by far common (as compared to other manifestations) there is a well-established [14] pathological evidence of past CoVs directly affecting the CNS. Indeed, severe acute respiratory syndrome-related coronavirus (SARS-CoV) was isolated from brain tissue suffering edema, with neuronal degeneration observed during autopsies through techniques such as immunohistochemistry, in situ hybridization, and electron microscopic confirmation of neuronal viral infection [15].

How is SARS-CoV-2 Infection Penetrating Directly into the CNS?

Different teams [16-18] have already shown with data coming from animal and clinical studies that CoVs are able to cross the blood-brain barrier (BBB) and penetrate into the CNS, causing neuronal invasion, and four different transmission routes for SARS-

CoV-2 neuronal CNS invasion have been suggested, in this respect: (1) Intranasal introduction of CoVs through olfactory neurons in the olfactory epithelium and mitral/tufted cells in the olfactory bulb. (2) BBB penetration via diapedes by infected monocytes. (3) Trans-synaptic transmission through nerves at the peripheral level. (4) Interaction between CoVs and Angiotensin-Converting Enzyme-2 (ACE2) receptors on BBB endothelial cells [19].

Distribution of ACE2 in the Human Brain

Even if the primary target cells for SARS-CoV-2 are the epithelial cells of the respiratory and gastrointestinal tract containing ACE2, the transmembrane protein serving as the main entry point into cells for some CoVs including SARS-CoV-2, there is existing evidence of the existence and distribution of ACE2 in the human brain, a fact that could indeed explain some of the COVID-19 neurological features reported so far.

In this regard, the expression and distribution of ACE2 in brain tissue has been recently investigated by performing an analysis of data available from public brain transcriptome databases [20]. As a result, the authors found that even if compared with the lungs the general expression of ACE2 in the brain was low, it was expressed in some important brain areas, such as the substantia nigra and/or brain ventricles. Conversely, ACE2-expressing cells were not expressed in the prefrontal cortex and only a few were expressed in the hippocampus. For the spatial distribution of ACE2 in the human brain, the same authors showed ACE2 high expressed in the dopaminergic nuclei including ventral tegmental area (VTA) and substantianigra, the serotonergic nuclei including midbrain raphe nuclei, histaminergic nuclei including tuberomammillary nucleus, and norepinephrinergic nuclei including locus ceruleus [20].

Another group recently showed through multi experiment matrix (MEM), a robust web tool allowing to integrate and combine correlation links between messenger RNA (mRNA) levels across human microarray datasets, that the gene exhibiting the most statistically significant co-expression link with ACE2 is Dopa Decarboxylase (DDC). As a result, the same group interestingly argues that DDC, as a major enzyme of the dopamine and the serotonin pathways, converts L-3,4-dihydroxyphenylalanine (L-DOPA) into dopamine, L-5-hydroxytryptophan into serotonin, and supports the conversion of histidine into histamine, and that, if ACE2 coregulates with DDC, it could indicate a possible functional link between the ACE2-mediated synthesis of angiotensin 1-7 and the DDC-mediated synthesis of dopamine and serotonin [21].

Could, as a result, an ACE2-DDC co-regulation imply a SARS-CoV2-induced downregulation of ACE2 expression, paired with important alterations of the dopamine and serotonin synthetic pathways?

In a similar line, it has been shown that ACE2 knockout (KO) mice were reported to exhibit low serotonin levels in the brain [22]. In view of the foregoing, it is possible to state that SARS-CoV-2 may be capable to directly infect and damage the brain, a fact leading to the serious CNS symptoms already seen in patients suffering COVID-19: "Once within the milieu of the neuronal tissues, the interaction SARS-CoV-2 with ACE2 receptors expressed in neurons can initiate a cycle of viral budding accompanied by neuronal damage without substantial inflammation, as has been seen with cases of SARS-CoV-1 in the past" [23]. If SARS-CoV-2 binds to ACE2 receptors, membrane

fusion and virus entry into the cell could lead to down-regulation of these receptors [24,25] with subsequent inflammatory lesions at the brain level, or neurotransmitter imbalances.

SARS-CoV-2 and the Pathophysiology of COVID-19-Related Delirium Symptomatology

Delirium, cognitive deficits and behavioural abnormalities in the context of COVID-19 are possibly caused by systemic inflammation and conditions of prolonged hypoxia, inducing the long-lasting and non-controlled neuronal inflammation cascade damaging areas such as the hippocampus and/or other cortical areas associated with the cognitive dysfunctions and the behavioural alterations presented by patients suffering delirium [5,6,10,13].

Even if research is extensive, and delirium is mainly characterized as being caused by systemic inflammatory condition, the actual mechanism of delirium is not clearly delineated. As we have already seen, the causes of delirium are frequently multifactorial and the result of stressors on multiple systems including immune/inflammatory, hormonal regulation via the hypothalamic-pituitary-adrenal and, notably, neurotransmitter regulation. In this sense, neurotransmitters are thought to be involved in delirium, and imbalances in the release, synthesis, and degradation of monoamines such as serotonin, norepinephrine, and dopamine have been linked, hypothetically, to the development of delirium [24].

For instance, serotonin is one of the major neurotransmitters in the brain, being its production in dependence to the precursor tryptophan (TRP) [24]. In this regard, patients who developed delirium after postoperative surgery had significantly lower levels of TRP than postoperative surgery patients who did not develop delirium [25].

Could it be postulated then, that a decrease in TRP levels may lead to a decrease in serotonin, which ultimately may lead to the development of delirium? And, importantly, could the latter be due to the SARS-CoV-2/ACE2 interaction at the neuronal level?

If SARS-CoV-2 binding to brain ACE2 receptors, with the consequent membrane fusion and virus entry into the cell, could lead to down-regulation of these receptors, in line with different authors and groups [26-28], with subsequent inflammatory lesions at the brain level, or different neurotransmitter imbalances, is a question to be resolved.

Conclusion

Here, we presented our point of view on the direct effects of the SARS-CoV-2 infection on the human CNS and its related cognitive and neuropsychiatric complications, aiming that the reviewed data will have guiding importance for the prevention and treatment of COVID-19. In this context, this work constitutes a renewed point of view for the study of the delirium-based COVID-19 physiopathology and could help to establish new and emerging causal links between SARS-CoV-2 infection, delirium, and its resulting neurocognitive alterations.

Author Contributions

Javier C Vázquez contributed substantially to the conception and design of the manuscript, acquisition of data, and data analysis

and interpretation, agreeing to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Javier C Vázquez and Diego Redolar-Ripoll drafted the manuscript. Diego Redolar-Ripoll provided critical revision of the article and final approval of the version to be published.

Declaration of Conflicting Interests

The author(s) declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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