Review article

How SARS-Cov-2 can involve the central nervous system. A systematic analysis of literature of the department of human neurosciences of Sapienza University, Italy

Daniele Armocida [b,*], Mauro Palmieri [b,*], Alessandro Frati [a], Antonio Santoro [a], Alessandro Pesce [a,b]

[a] IRCCS – "Neuromed", Pozzilli, (IS), Italy
[b] A.U.O. "Policlinico Umberto I", Neurosurgery Division, Sapienza University, Rome Human Neurosciences Department, Via del Policlinico, 155 – 00161 Rome, Italy

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ABSTRACT

Italy is currently one of the countries most affected by the global emergency of COVID-19, a lethal disease of a novel coronavirus renamed as SARS-CoV-2. SARS-CoV-2 shares highly homological sequence with the most studied SARS-CoV, and causes acute, highly deadly pneumonia (COVID-19) with clinical symptoms similar to those reported for SARS-CoV and MERS-CoV. Increasing evidence shows that these coronaviruses are not always confined to the respiratory tract and that they may also neuroinvasive and neurotropic, with potential neuropathological consequences in vulnerable populations. The aim of this study is to predict a likely CNS involvement by SARS-CoV-2 by studying the pathogenic mechanisms in common with other better known and studied coronaviruses with which it shares the same characteristics.

Understanding the mechanisms of neuroinvasion and interaction of HCoV (including SARS-Cov-2) with the CNS is essential to evaluate potentially pathological short- and long-term consequences. Autopsies of the COVID-19 patients, detailed neurological investigation, and attempts to isolate SARS-CoV-2 from the endothelium of cerebral microcirculation, cerebrospinal fluid, glial cells, and neuronal tissue can clarify the role played by COVID-19 in CNS-involvement and in the ongoing mortalities as has been in the recent outbreak.

1. Introduction

Another highly pathogenic HCoV, currently called SARS-CoV-2, emerged in December 2019 in Wuhan, China, and spread rapidly around the world involving Europe and especially Italy in a dramatic way [79]. This novel HCoV has caused a national outbreak of severe pandemic pneumonia (COVID-19). The first reports about a dangerous infection emerged from December 2019 in Wuhan, China. In February 2020, a designation "severe acute respiratory syndrome coronavirus 2" (SARS-CoV-2) became the official means to refer to this type of virus, and finally, the WHO officially renamed the disease as COVID-19. The complete genome of SARS-CoV-2 was successfully established as 29,903 bp single-stranded RNA (ss-RNA) SARS-like coronavirus [1]. Italy is currently one of the countries most affected by the global emergency of COVID-19.

The common onset-symptoms of COVID-19 are dry cough and fever at the onset of illness, but rapidly pathology evolves towards a respiratory distress syndrome (ARDS), and most of the patients admitted to the intensive care could not breathe spontaneously. About 46% ~ 65% of the patients in the intensive care worsened in a short period and died due to respiratory failure [63].

As observed for the most important pandemic circulating strains of HCoVs they involve more frequently a vulnerable population (such as the elderly, immune-compromised individuals or patients with comorbidities). Additionally, it has been reported that some patients affected by SARS-CoV-2 also showed neurologic signs such as headache, nausea, and vomiting [2–4,69].

Recently, a study from Mao et al. [77] has reported neurological manifestations in COVID-19 which suggests a rationale of the neurotropic potential in the COVID-19 virus. Also, recently it was reported [70] a suspected first European case of COVID-19 associated with acute necrotizing hemorrhagic encephalopathy in a female airline worker.

A lot of studies demonstrate that HCoVs can invade the CNS [6,38,39] and that neurotropism is one common feature of these groups of virus [44]. Recent findings of an altered sense of smell or hyposmia in an uncomplicated early stage of COVID- 19 have been reported, and these data should be investigated thoroughly for CNS involvement.

The aim of this study is to predict a likely CNS involvement by SARS-CoV-2 by studying the pathogenic mechanisms in common with other better known and studied coronaviruses with which it shares the same characteristics.

2. Material and methods

2.1. Rationale

In light of the high similarity between SARS-CoV and SARS-CoV2, the potential neuro-invasion of SARS-CoV-2 is likely linked to the acute respiratory failure of COVID-19 patients. Some studies demonstrate a critical role for infection of the CNS in severe disease in SARS-CoV-infected animals and humans [4,76].

2.2. Objective

Being that most HCoVs share a similar viral structure and infection pathway and therefore the infection mechanisms previously found for other HCoVs, it is reasonable that previously studied hypothetical mechanisms of neuro-invasion may also be applicable for SARS-CoV-2.

Based on an epidemiological survey on COVID-19, the median time from the first symptom to dyspnea was 5.0 days, and to the intensive care was 8.0 days 5. Therefore, given the probable neuro-invasion, the latency period is enough for the virus to enter into the neurons and the risk of SARS-CoV-2 infection may be currently underestimated. As an emerging virus no effective treatment has been developed for the COVID-19. Therefore, awareness of the possible entry of SARS-CoV-2 into the CNS will have important guiding significance for the prevention and treatment.

2.3. Eligibility criteria: sources and study selection

Therefore, while screening the literature, we adopted the following inclusion and exclusion criteria: 1) papers identifying tropism to the central nervous system of the coronavirus family; 2) detailed reports concerning mechanisms of action, clinical and laboratory evaluation 3) year of publishing was also included to understand a possible year of experience/improvement of the technologic setup effect on the results;

Conversely, we excluded the following. First, we excluded articles that do not mention CSN involvement. Second, we excluded incomplete reports according to the aforementioned end points. Because accurate reports are extremely few, and among them, some focused predominantly on the involvement of respiratory tract and clinical surveillance, we decided to include in this review those reports in which at least 1 of the 2 key point about this topic of the present study were reported in detail.

2.4. Information sources

The English literature was systematically investigated using MEDLINE, the NIH Library, PubMed, and Google Scholar. The last search date was April 18, 2020. The following search terms were used: SARS-Cov central nervous system, SARS-CoV brain, coronavirus central nervous system, COVID-19 central nervous system and brain.

Backward citation tracking was applied to identify articles not retrieved by electronic searches. The search returned a total of 80 papers, 17 including review, 2 clinical trial and 61 laboratory study analysis.

To this initial cohort, the aforementioned exclusion criteria were applied, accordingly eliminating a total of 11 papers (Fig. 1). To this cohort of patients, the personal experience of our department and articles and case reports that hypothesize the specific involvement of SARS-CoV-2 of the CNS of the present paper were added, resulting in a total final cohort composed of 80 papers.

3. Discussion

3.1. The human coronaviruses naturally reach the central nervous system

Following the severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV), another highly pathogenic coronavirus named SARS-CoV-2 rapidly spreads around the world.

Human coronaviruses (HCoVs), which are large enveloped non-segmented positive-sense RNA viruses, generally cause enteric and respiratory diseases in animals and humans [57].

HCoVs are typically classified in two groups: Alphacoronavirus (of which the most representative is HCoV-229E) and Betacoronavirus (HCoV-OC43, SARS-and MERS-CoV) 24

HCoVs can reach the lower respiratory tract and, as opportunistic pathogens [14,65,66], be associated with more severe illnesses, such as bronchitis, bronchiolitis, pneumonia and ARDS as it happened for SARS-CoV and MERS-CoV, has called global attention to the lethal potential of HCoVs [58]. So, genomic analysis and public evidence show that SARS-CoV-2 is in the same Betacoronavirus group as MERS-CoV and SARS-CoV, which shares a highly homological sequence with SARS-CoV [59], and shares similar pathogenesis [60]. Moreover, the entry of SARS-CoV-2 into human host cells has been identified to use the same entry receptor as SARS-CoV, suggesting the likelihood of the same population of cells being targeted and infected [25,61,62,71].

The entry of SARS-CoVs into human host cells is mediated mainly by a cellular receptor angiotensin-converting enzyme 2 (ACE2) which is expressed in human airway epithelia, lung parenchyma, vascular endothelia, kidney cells, and small intestine cells.
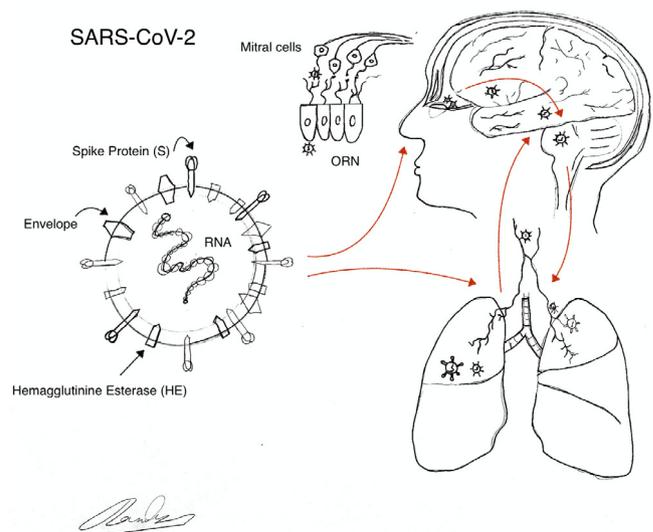

Fig. 1. A prisma Flow-diagram for selection of studies.

Primary viral replication takes place in the mucosal epithelium of upper respiratory tract (nasal cavity and pharynx), with further multiplication in the lower respiratory tract and gastrointestinal mucosa [72], giving rise to a mild viremia.

Dissimilar to SARS-CoV, SARS-CoV-2-infected patients rarely showed prominent upper respiratory tract signs and symptoms, but manifest an exuberant inflammatory response during SARS-CoV-2 infection, further resulting in uncontrolled pulmonary inflammation, likely a leading cause of case fatality, indicating that the target cells of SARS-CoV-2 may be located in the lower airway [58]. Rapid viral replication and cellular damage, virus-induced ACE2 downregulation and shedding, and antibody-dependent enhancement (ADE) are responsible for the development of an aggressive inflammation caused by SARS-CoV-2 [71]. The initial onset of rapid viral replication may trigger the production of exuberant pro-inflammatory cytokines and chemokines. A possible underlying mechanism of antibody-dependent enhancement (ADE) has been proposed recently [71] as the phenomenon that can promote viral cellular uptake of an infectious virus–antibody complexes following their interaction with Fc receptors (FcR), FcγR, or other receptors, resulting in enhanced infection of target cells. The interaction of FcγR with the virus-anti-S protein-neutralizing antibodies (anti-S-IgG) complex may facilitate both inflammatory responses and persistent viral replication in the lungs [25,71].

Viral involvements of the CNS are rare and often the clinical surveillance focus on a few different viruses such as HSV, arboviruses, and enteroviruses [10], but HCoVs also have a recognized ability to invade the CNS, where they can infect the neurons [3], but their incidence in clinical practice is difficult to evaluate [11]. HCoVs can naturally reach the CNS in humans and could potentially be associated with neurological symptoms [6,25,28,33]. These ubiquitous human pathogens are molecularly related in structure and mode of replication that is the same for every type [16–20].

3.2. The route to the CNS

Over the years, HCoVs have also been identified as possible etiological agents for pathologies outside the respiratory tract [25–27] and a propensity, under certain conditions, to invade the CNS [57,64] and induce neurological diseases [28–30]. However, the exact route by HCoVs enters the CNS is still not completely understood. HCoV may enter the CNS through different hypothesized ways.

The main theory affirm that SARS-CoV probably uses as the main entry route into the CNS the olfactory nerve fibers [4,15,31,32,48], and induces neuronal cell death [4]. In the human airways, after an intranasal infection, although the olfactory bulb is highly efficient to controlling viral neuro-invasion, HCoVs have been shown to enter CNS through the olfactory route (OR) [41–43] (in same pathway both animal and humans [22,23]).

The virus in the general circulation enables it to pass into the cerebral circulation where the sluggish movement of the blood within the microcirculation combined with the high rate of load in initial sites of infection could be one of the factors make possible the interaction of the COVID-19 virus spike protein (S-protein) with ACE2 expressed in the capillary endothelium. Subsequent budding of the viral particles from the capillary endothelium, spreading along the Virchow-Robin spaces surrounding arterioles and venules [2,44], and disseminates to several different regions of the brain and the brainstem [39,43].

The second hypothesized pattern of spreading within the CNS is through neuronal dissemination, where a given virus infects neurons in the periphery using the mechanisms of active transport within those cells to gain access to the CNS [39,40,44,50,52]. Seems

that HCoV could move along the axon using the anterograde axonal transport between neurons without an effective inflammation of tissue [49]. Other details are described in the schematic draw (Fig. 2).

SARS-CoV, also demonstrates a potential myeloid cell invasion [34–36] and an ability to manipulate the innate immunity and to disseminate to other tissues, including the CNS [37]. Moreover, persistently-infected leukocytes may serve as a reservoir and vector for neuroinvasive HCoV [38]. Although HCoV infections are, most of the time, restricted to the airways, they may under poorly understood conditions extend over the epithelium barrier and could use the hematogenous route propagate towards the CNS [33]; However, the hematogenous or lymphatic route seems impossible, especially in the early stage of infection, since almost no virus particle was detected in the non-neuronal cells in the infected brain areas [68].

Specifically for COVID-19, the possible neuro-invasion of SARS-CoV-2 may also partially explain why some of the patients developed respiratory failure. It is possible that most of the persons in Wuhan, who were the first exposed to this previously unknown virus, did not have any protective measure so that the mortality rate in Wuhan was higher than in other cities in China. On the other hand, is hard to explain the high number of deaths and critical patients in Italy. If the neuro-invasion of SARS-CoV-2 does play a role in the development of respiratory failure in COVID-19 patients, the precautionary use of masks could be considered as the most effective measure to protect against the possible entry of the virus into the CNS. The presence of HCoVs viral particles
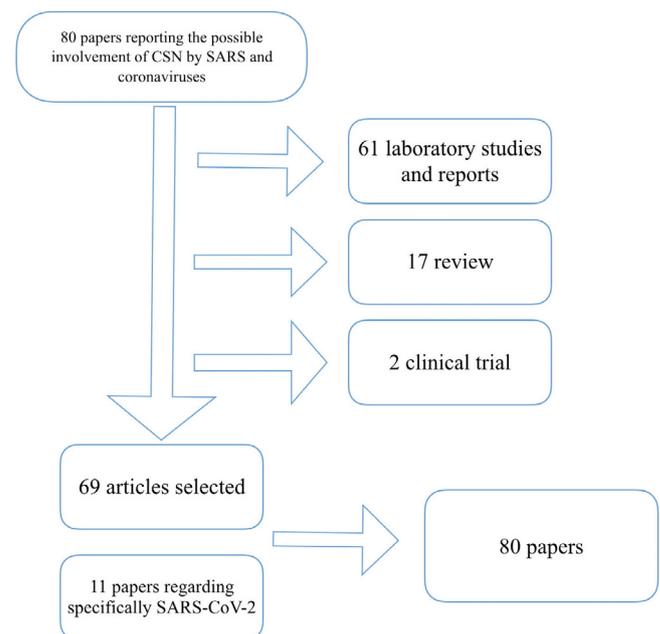

Fig. 2. A schematic representation of the possible spreading of SARS-CoV-2 to CSN drawn by the author. SARS-COV-2 uses severals mRNA encoding proteins, such S1 protein that enables the attachment of the virion to the cell membrane by interacting with the host ACE2 receptor. Viral S and E proteins, structural and accessory proteins are important factors of neurovirulence, neuropropagation and neurodegeneration of infected cells. HCoV may lead to the disruption of the nasal epithelium and across the cribriform plate of the ethmoid bone close to the olfactory bulb uses as the main entry route into the CNS the olfactory nerve fibers. The virus disseminates to several different regions of the brain and the brainstem via a synapse-connected route to the medullary cardiorespiratory center, may also partially explain why some of the patients developed respiratory failure (upper part of scheme). The second hypothesized pattern of spreading within the CNS is through neuronal dissemination, where a given virus infects neurons in the periphery using the mechanisms of active transport within those cells to gain access to the CNS (lower part of scheme).

has been reported in the brains of patients and experimental animals, where the brainstem was heavily infected. In light of the similar nature between SARS-CoV and SARS-CoV2, the potential invasion of SARS-CoV2 is likely partially responsible for the ARDS in COVID-19 patients. Awareness of this will have important guiding significance for the prevention and treatment of the SARS-CoV-2-induced respiratory failure. Besides all these issues, accumulating evidence from the medical world strongly suggests that, being opportunistic pathogens, these viruses can escape the immune response and spread to the CNS [12,13].

3.3. Possible mechanisms

The brain has been reported to express ACE2 receptors that have been detected over glial cells and neurons, which makes them a potential target of SARS-CoVs where its interaction with ACE2 receptors expressed in neurons can initiate a cycle of viral budding [21]. SARS-COV-2, like SARS-CoV, uses other mRNA encoding several proteins, such S1protein [52] that enables the attachment of the virion to the cell membrane by interacting with the host ACE2 receptor.

Viral budding in the brain can be accompanied by neuronal damage without substantial inflammation, or by a large endothelial rupture in cerebral capillaries accompanied by bleeding within the cerebral tissue [22]. The role of the blood–brain barrier (BBB) in containing the virus and preventing it from gaining access to the neural tissues [9] and type of spreading needs to be further explored. The presence of ACE2 or DPP4 solely is not sufficient to make host cells susceptible to infection. For example, some ACE2-expressing endothelial cells failed to be infected by SARS-CoV [67]. Likewise, the infection of SARS-CoV or MERS-CoV was also reported in the CNS, where the expression level of ACE2 or DDP4 is very low under normal conditions.

ACE2 binding affinity of the SARS-CoV-2 S-protein ectodomain was 10–20-fold higher than that of the SARS-CoV S-protein, which may be the reason for the higher binding affinity of the COVID-19 S-protein to the human ACE2 receptor in lower respiratory tract.

The structural proteins S and E proteins are actually consider the most important factor of neurovirulence and propagation in virus-cell interactions [6,7,50,52]. S proteins (in particular S2 and S5 domain), play a significant role in viral dissemination and influence the rate and success of virus propagation towards the brain [44].

It's reported that a single point mutation in S-protein of HCoV-OC43 modulates virus-induced neuropathology in a mouse model from encephalitis to an MS-like paralytic disease related to glutamate excitotoxicity, with the involvement of AMPA receptors [73]. It was demonstrated that glutamate receptors are also involved in the infection of mice with HCoV-OC43. Possible glutamate excitotoxicity, thus increasing damage to neurons and/or disturbing glutamate homeostasis [6,7] and thereby contributing to neuronal degeneration and hind-limb paralysis and possible demyelination [44].

It is also possible that excessive levels of proinflammatory cytokines/chemokines in the brain result in a "cytokine storm" that can lead to harmful effects in the brain and other tissues. To support this hypothesis, three cytokines often associated with immunopathology, IL-1, tumor necrosis factor-alpha, and IL-6, are all upregulated in the brains of infected K18-hACE2 mice [76]. IL-6 was produced by a normal consequence of infected neurons and in the adult brain following ischemia in an unknown mechanism. Probably, IL-6 may be induced by another inflammatory mediator, such as IL-1 or tumor necrosis factor alpha [78], also expressed in the SARS-CoV-infected CNS.

Given this high-level expression of proinflammatory mediators, the lack of inflammation that we often observe in the CNS is surprising [38].

One possibility is that the virus interferes with the initiation of the immune response is not known at present but may be one mechanism that would result in a diminished inflammatory response [33,44].

The other one is that the degeneration of neurons may successfully lead to to the induction of different regulated cell death (RCD) pathways [34,53], similar of what observed after infection by other respiratory viruses [50,51].

4. Limitations and future studies

In the SARS-CoV infections that were reported in the past, autopsy findings of the patients have shown strong shreds of evidence of the presence of SARS-CoV by electron microscopy, immunohistochemistry, and real-time reverse transcription-PCR. Patients with acute SARS-CoV illness have also demonstrated the presence of the virus in cerebrospinal fluid [5], but currently, due to high health security measures, there is no availability of autopsy studies.

In conclusion, there is not a clear cause-and-effect relationship with the onset of neurological symptoms in COVID-19 patients, though recent reports associated cases of CNS-involving [6,8,9,28]. HCoV may potentially persist in the human CNS as it does in murine models and potentially be associated with different types of long-term sequelae and chronic human neurological diseases [45-47], Such questions deserve timely investigations.

Viral encephalitis is often caused by herpes simplex and other types of viruses [74,75]. The brain lesions are often hemorrhagic [54], and a rare complication is a large intracerebral hematoma which usually implies a poor prognosis. For this reason MRI can be a perfect tool to identify a viral propagation in brain [74,75]

The prognosis of viral encephalitis is usually poor, but early treatment with antiviral agents has been proven to be efficacious, the challenge is that with such a rapid worsening of onset symptoms that required assisted ventilation, COVID-19 patients are often not neurologically evaluable and therefore it is difficult to discriminate which of them would indicate to perform neuroimaging. Furthermore, the potential neurological significance of the typical hypo-ageusia and hypo-anosmia of COVID-19[14] was until now, systematically investigated through MRI imaging.

Actually we don't know how viral factors (mutations in specific virulence genes), host factors (immunodepression, age) or a mixture of both (underlining the importance of virus-host interactions) [39,55,56] can explain the access of HCoV to the CNS. Autopsies of the COVID-19 patients, detailed neurological investigation, and attempts to isolate SARS-CoV-2 from the endothelium of cerebral microcirculation, cerebrospinal fluid, glial cells, and neuronal tissue would clarify the role played by this novel COVID-19 causing coronavirus in the ongoing mortalities as has been in the recent outbreak.

5. Conclusion

The neurotropic potential of SARS-CoV-2 in patients reported in the recent outbreak of COVID-19 has to be considered as a potentially serious threat for all health care systems, worldwide. Accumulating evidence indicates that HCoVs are neuroinvasive in humans and we hypothesize represent an important proportion of CNS viral infection associated with encephalitis, meningitis, myelitis, and long-term neurological disorders, either as a result of inadequate host immune responses and/or viral propagation in the CNS and for this reason COVID-19 will need to be studied for a long time even after the Italian and European health emergency is overcome to avoid possible other fearsome consequences for public health. Understanding the mechanisms of neuroinvasion

and interaction of SARS-HCoV-2 with the CNS is essential to evaluate potentially pathological short- and long-term consequences. Antiviral therapy should be carried out as early as possible and it is also urgent to find effective antiviral drugs that can cross the BBB.

Compliance with ethical standards

Funding: This study was no funded by any association.

Conflict of interest: We wish to confirm that there are no known conflicts of interest associated with this publication and there has been no significant financial support for this work that could have influenced its outcome. We wish to draw the attention of the Editor to the following facts which may be considered as potential conflicts of interest and to significant financial contributions to this work.

Ethical approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

This article does not contain any studies with animals performed by any of the authors.

Informed consent: Informed consent was obtained from all individual participants included in the study.

The patient has consented to the submission of this review article to the journal.

We confirm that the manuscript has been read and approved by all named authors and that there are no other persons who satisfied the criteria for authorship but are not listed. We further confirm that the order of authors listed in the manuscript has been approved by all of us.

We confirm that we have given due consideration to the protection of intellectual property associated with this work and that there are no impediments to publication, including the timing of publication, with respect to intellectual property. In so doing we confirm that we have followed the regulations of our institutions concerning intellectual property.

We further confirm that any aspect of the work covered in this manuscript that has involved either experimental animals or human patients has been conducted with the ethical approval of all relevant bodies and that such approvals are acknowledged within the manuscript.

We understand that the Corresponding Author is the sole contact for the Editorial process (including Editorial Manager and direct communications with the office). He/she is responsible for communicating with the other authors about progress, submissions of revisions and final approval of proofs. We confirm that we have provided a current, correct email address which is accessible by the Corresponding Author and which has been configured to accept email.

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Further reading

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