Novel Coronavirus Disease (COVID-19) and Central Nervous System Complications: What Neurologist Need to Know

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Abstract

The novel coronavirus (Covid-19) is a family of large enveloped non-segmented positive-sense RNA viruses which has been considered as a global health concern as it has a very high transmissibility potential. Regarding to the similarity of the virus to SARS-CoV, it is postulated that the Covid-19 accumulates mainly in the nasal epithelia and lower respiratory airways. However, there is evidence suggesting the Covid-19 neurotropism which might contribute to respiratory failure. Here in we aim to review the central nervous system complications of the Covid-19 CoV since the emergence of the virus.

Keywords: Novel Coronavirus, Covid19-Cov, CNS Complication, Nervous System

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INTRODUCTION

The novel coronavirus (2019-nCoV / Covid-19 CoV) has been declared as a public health emergency of international concern by World Health Organization (WHO) as it has a significant potential for transmissibility [(1)].

The Covid-19 CoV is a family of large enveloped non-segmented positive-sense RNA viruses in the same subgenus with severe acute respiratory syndrome CoV (SARS-CoV), but in different clade[(1)]. It was first reported in December 2019 in Wuhan, China with a cluster of unexplained pneumonia which soon has turned into a global health concern[(2)]. According to WHO, the Covid-19 CoV is considered as the fast contagious coronavirus worldwide affecting approximately 332930 cases across 195 countries so far which is now declared as a global pandemic[(3,4)]. Similar to SARS-CoV, the main entry of the Covid-19 CoV into human host seems to be mediated 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. However, there are reports of viral central nervous system (CNS) infection, where the expression level of ACE2 is very low[(5-8)]. Given the rapid spread, long term persistence and neuro-virulence of the

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virus, here in this literature review, we aimed to provide the most information available on CNS complications of the Covid-19 CoV since the emergence of the virus.

METHODS

This study was carried out in databases such as PubMed, Scopus, Web of Science, Ovid, ProQuest, Wiley, ScienceDirect and Springer. We used the MeSH keywords (Coronavirus* OR covid* OR Cov*) AND (CNS OR central nervous system) AND (neuro* OR nerv*) in title, abstract and keywords. We searched for all randomized controlled trials (RCTs), in vitro and animal studies in all over the world until 23 March 2020 to review virology, pathogenesis, neurological manifestations, neurologic complications and mechanism of neuropathogenesis for Betacoronaviruses and the 2019 novel Coronavirus (COVID-19). Studies that examined non-Betacoronaviruses were excluded. One independent reviewer searched with focusing on Betacoronaviruses and the 2019 novel Coronavirus (COVID-19). Other independent reviewer searched around central nervous systems complications and manifestations. This study is accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.

RESULTS

Virology and pathogenesis:

Coronaviruses are enveloped non-segmented positive stranded RNA viruses belonging to the family Coronaviridae [9]. They encode a set of four structural proteins, namely; spike glycoprotein (S), small envelope protein (E), membrane glycoprotein (M) and nucleocapsid proteins (N). The spike glycoprotein (S glycoprotein), which plays a dominant role in host attachment is cleaved by a host cell furin-like protease into two separate polypeptides S1 and S2 [10,11]. Some CoVs have an extra furin cleavage site (RRKR/S, furin-S20 site) upstream of the fusion peptide in the spike protein contributing to virion adsorption [12–14]. Although most subtypes of this family as hCoV-229E, OC43, NL63, and HKU1, cause mild respiratory diseases, the three highly pathogenic coronaviruses, the SARS-CoV, Middle East respiratory syndrome CoV (MERS-CoV) and newly emerging Covid-19 CoV have called the global attention to the fatal potential [15]. Regarding to the similarities of Covid-19 CoV receptor binding domain sequence to SARS-CoV, ACE2 is postulated as the functional receptor for Covid-19 CoV which is expressed mainly in the airway epithelia, lung parenchyma, vascular endothelia, kidney cells, and small intestine cells [5–8]. As the ACE2 level is very low in the central nervous system, there should be other mechanisms to justify the neurotropism of Covid-19 CoV as there is a report of laboratory confirmed Covid-19 CoV with the first manifestation being acute third neve palsy [16]. Of note, the molecular and cellular basis of coronavirus neuro-virulence is poorly understood. Nevertheless, the greatest tendency for neuro-invasion is observed in some subgenus as mouse hepatitis virus John Howard Mueller strain (MHV-JHM), human coronavirus OC43 (HCoV-OC43) and Avain infectious bronchitis virus (IBV) [17,18].

Epidemiology:

The first case of the Covid-19CoV epidemic was discovered with unexplained pneumonia on December 12, 2019 in Wuhan, china which rose to 27 patients with seven being severe, confirmed by Health Commission of Hubei province, China, on December 31, 2019 [2,19]. Subsequently, one death was reported on January 11, 2020 which prompted a significant attention to the infection [2]. It was estimated that the virus had a reproductive number of approximately 1.4 - 5.5 which was significantly higher than SARS-CoV and MERS-CoV[1]. On January 22, 2020, the wild bat was identified as the origin of Covid-19 CoV. Based on the first reports in Wuhan, in the first phase of the outbreak, the majority of patients was men with a median age of 55 years and linked to the Huanan seafood Wholesale market. However, the second phase of outbreak occurred following a human-to-human transmission leading to a widespread viral propagation [20,21].

The first non-Chinese case of the infection, was reported from Thailand on January 13, 2020 in a Chinese tourist who had traveled to Thailand without any epidemiologic connection with the marketplace [22]. As of February 25, 2020, a total of 81,109 laboratory confirmed cases had been documented globally and now, based on the latest date 23 March 2020, the Covid-19 CoV is affecting 195 countries and territories around the world with a total

cases of 332930 and total death of 14510 in which Italy and United States are the most affected countries after China respectively [3,4,23,24].

Clinical manifestations:

Covid-19CoV infection shares many clinical similarities with infection caused by SARS-CoV and MERS-CoV. Following an incubation period of 3-14 days, the non-specific symptoms such as malaise, fever, and dry cough will appear. Depending on the patient's immunity system level and concurrent comorbidities, the symptoms might remain mild or lead to severe course and even death. Pneumonia appears to be the most frequent serious manifestation characterized by fever, dry cough and dyspnea [19,24–28]. In a report of 44500 cases from the chines center for disease control and prevention, 81% of patients were classified into mild (non-pneumonia or mild pneumonia), 14% severe (dyspnea, respiratory frequency ≥30/min, blood oxygen saturation ≤93%, partial pressure of arterial oxygen to fraction of inspired oxygen ratio <300, and/or lung infiltrates >50% within 24-48 hours) and 5% critical(respiratory failure, septic shock, and/or multiple organ dysfunction) with a fatality rate of 2.3% [29]. In terms of non-respiratory complications, the involvement of intestinal tract, renal, hepatic, cardiovascular system, CNS and lymphocytopenia have been reported. It is noteworthy, in contrast to SARS-CoV the intestinal and renal manifestation less frequently occurs [25].

Neurologic complications:

The data on neurologic symptoms of patients with Covid-19 CoV is limited. According to the study of Lingo et al on 214 patients, the CNS and peripheral nerve system (PNS) involvement was observed in 24.8% and 8.9% of the patients, respectively which were both more evident in severe cases. The main CNS symptoms were dizziness (16.8%) and headache (13.1%). Other CNS complications were impaired consciousness, acute ischemic stroke and intracranial hemorrhage. Additionally, the main PNS symptoms were hypogeusia (5.6%) and hyposmia (5.1%) [30]. It should be noted that, seven of our Covid-19 patients who were all classified as mild cases, were complicated with hyposmia and hypogeusia over hospitalization. Interestingly, the Covid-19 CoV polymerase chain reaction (PCR) test was positive for two of our health care givers who had a close contact with Covid-19 CoV patients and complained of persistent and unexplained hyposmia.

More ever, there is a report of a 74-year-old male with past medical history of atrial fibrillation, cardio-embolic stroke, parkinson disease, chronic obstructive pulmonary disease (COPD), presenting with a progressive fever and productive cough who was first diagnosed with COPD exacerbation. However, over 24 hours, his symptoms deteriorated accompanied with confusional state and disorientation. In his second hospitalization he was transferred to the intensive care unit and needed intubation. A lumbar puncture did not reveal any evidence of central nervous system infection. As the encephalopathy was not clearly explained by metabolic and hypoxic etiologies, the suspicion of Covid-19 CoV was proposed and the patient was eventually diagnosed with Covid-19 CoV [31].

Interestingly, there is a report of Covid-19 CoV patient with a rare presentation. The primary manifestation leading to admission was third nerve palsy. However, on hospital day 2, the characteristic features progressively evolved with fever and dyspnea [16]. It is noteworthy that, more data is needed to confirm the association of cranial nerve palsy and Covid-19 CoV infection.

Similarly, we had a patient who first admitted to the hospital for persistent positional vertigo. However, due to a history of malaise and sore throat, he went under chest computed topography (CT) revealing diffuse ground glass opacities in both lungs. He was eventually diagnosed with mild Covid-19 CoV disease with a complete recovery.

The neurological manifestations of Covid-19 Cov of all the reviewed articles are summarized in table 1.

Mechanism of neuropathogenesis

Our knowledge of in vivo model of human CoV neuro-virulence is mainly based on the natural susceptibility of mice to HCoV-OC43 and MHV[17,18,32]. In 1944, a report from F. Sargent Cheever et al revealed the evidence of disseminated encephalomyelitis with extensive destruction of the myelin induced by inoculation of JHM virus in murine model which shed light on the pathway to CoV neuropathogenesis discovery [33]. The next experimental models focused on the pathogenesis of the CoV neurotropism which were suggestive of a mutation of the envelope spike (S) glycoprotein as a mutation at the

S2′ site of QX genotype (QX-type) infectious IBV spike protein (S) in a recombinant virus or a mutation at amino acid 758 (G758R) of infectious HCoV-OC43 envelope spike (S) glycoprotein in a recombinant virus creating a functional cleavage between the S1 and S2 portions of the S protein [12,34–36] Additionally, there was evidence suggesting the role of pro-inflammatory cytokines as interleukin 12(IL-12), tumor necrosis factor alpha, IL-6, IL-15, IL-1β and IFNα/β signaling induced by astrocytes and microglia dealing with the virus [37,38].

With the advent of SARS-CoV and MERS-CoV, the neuro-virulence of the newly emerging CoVs was highlighted. The primary experimental studies using transgenic mice demonstrated that either SARS-CoV or MERS-COV, when given intra-nasally, was capable to infect the brain. Additionally, it was declared that the thalamus and brainstem neurons were the most susceptible targets and the their dysfunction could lead to death which were more prominent for those located in cardiorespiratory centers in the medulla [39].

In the following, the human models were investigated. In one report, histopathologic examination of autopsy samples from eight SARS patients demonstrated the presence of SARS-CoV particles in the cytoplasm of numerous neurons in the hypothalamus and cortex [40] Similar studies using immunohistochemistry revealed the SARS-CoV particles in the brain tissue of patients with SARS [41,42]. Additionally, in one report the SARS-CoV was detected in the cerebrospinal fluid of a patient with neurological sequel following SARS infection [43].

In order to discover the neurovirulence of Covid-19 CoV, the primary attention has been turned into the similarities and differences of the newly emerging virus from SARS-CoV at the genomic and transcriptomic level. Regarding to the similarities of Covid-19 CoV receptor binding domain sequence to SARS-CoV, ACE2 is postulated as the main receptor for Covid-19 CoV. Most of the evidence of ACE2 expression by the glial cells and neurons in the brain prompted the clinicians toward the neurotropism of the Covid-19 CoV [5–8,44]. Recently, a more comprehensive study has conducted focusing on the neuro-invasive potential of Covid-19 CoV which was consistent with the previous studies showing the same mechanism of neuro-invasion and the potential for respiratory failure induced by viral propagation via a synapse-connected route to the medullary cardiorespiratory center from the mechano /chemo receptors in the lower respiratory airways [45]. However it should be noted that no evidence of Covid-19 CoV particles has been revealed in the cerebrospinal fluid of the Covid-19 CoV patients in the recently reported articles.

Taking all together, regarding to the abundance of ACE2 receptors in nasal epithelium, Covid-19 CoV is usually restricted to nasal epithelium and the lower respiratory airways. Nevertheless, under poorly understood conditions, it could pass through the epithelium barrier and reach the bloodstream or lymph leading to propagation towards the CNS [46]. on the other hand, there is a probability to enter the CNS through neuronal dissemination via olfactory bulb or cranial peripheral nerves [47–49]. Remarkably, regardless how the virus enters the brain, the virus preferably affects the neuronal cells contributing to neurological complications and even respiratory failure in case of cardiovascular

Table 1. The summary of neurological manifestations of Covid-19 Cov of all the reviewed articles

Article	Number of patients	Neurological manifestation	
Lingo Mao et al [30]	72	CNS involvement (53 patients)	Dizziness Headache Impaired consciousness Acute ischemic stroke Intracranial hemorrhage
		PNS involvement (19 patients)	Hypogeusia hyposmia
Asia Filatov et al [31]	Case report	encephalopathy	
Wei H et al [16]	Case report	Third nerve palsy	

center involvement in the medulla [49].

Taking into account the CNS complications of this newly emerging virus, more attention has to be taken to neurological examination of the Covid-19 CoV patients, as it might infect the cardiorespiratory centers leading to respiratory failure. Additionally, if the association of the hyposmia and neurologic complications of Covid-19 will be confirmed in future studies, there might be chance to detect the carriers in early stages which is in paramount of importance among the health care workers, as the hospitals are considered as one of the main source of viral propagation.

CONCLUSION

The novel coronavirus is a family of enveloped non-segmented positive stranded RNA viruses which shares a significant genomic similarities with SARS-CoV. It is hypothesized that, ACE2 is the functional receptor for Covid-19 CoV which is responsible for the main symptom as respiratory complications. However, under poorly understood conditions, the virus could enter the CNS with a higher vulnerability of the thalamus and brain stem neurons which could have a role on respiratory failure.

ETHICS

In addition, it should be noted that the informed consent was obtained by the patients of our center for publication.

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