Neurological Manifestations in COVID-19 Population: A Short Review

Kamal Pratap Singh1 and Rachna Agarwal1

Abstract

Background: Coronaviruses (CoVs) have a neuroinvasive potential, which has been discussed in various research papers. During the current pandemic, the novel CoV, i.e., SARS-CoV-2, is causing a considerable number of fatalities and posing a great danger of a recurrent epidemic. COVID-19 has been labeled as a public health emergency of international concern, and the epidemic curves are on the rise.

Purpose: Some studies discuss the neurological implications of SARS-CoV-2 but in light of growing number of evidences we cannot ignore the planning of mental health care settings in COVID-19. We are discussing how this novel CoV can affect the human brain directly and indirectly, including psychiatric problems, and how neurological conditions can be explored as a diagnostic tool in COVID-19 by analyzing cohort studies and review papers that discuss the recent neurological findings in COVID-19.

Method: Current research and review papers were searched to find out any relation between the COVID-19 disease and the altered mental health. This study attempts to find out neurological symptoms in a large population affected by COVID-19 and thus filtering out individual case reports and cohort studies which have a patient pool of less than 50.

Results: This unique observation revealed that SARS-CoV-2 has direct neurological manifestations such as anosmia and gustatory impairment, encephalopathy, and seizures as well as an indirect effect on the psychiatric health such as anxiety, amnesia, etc. because of psychosocial stress.

Conclusion: The most commonly reported neurological symptoms should not be ignored and must be tested for COVID-19. More neurological studies like medical imaging and neuropathology should be performed on these COVID-19 patients.

Keywords
Coronavirus, COVID-19, neuroinvasion, neurology, neuroimaging

Received 18 October 2020; accepted 27 October 2020

Introduction

Coronaviruses (CoVs) were first identified during an infection in chicks in 1931 and named the avian infectious bronchitis virus. Later, such viruses were also reported as human pathogens in a common cold infection. Extensive research by T Estola and many other scientists from years 1930 to 1975 and a growing number of respiratory viruses compelled scientific leaders to constitute a separate group of viruses. Subsequently, after several discussions among virologists a new family of viruses Coronaviridae, with one genus, was created in 1975. CoVs were further divided into four subtypes, i.e., alpha, beta, gamma, and delta CoVs. The novel SARS-CoV-2 is a beta CoV.

The first case of a CoV disease was notified as cold in 1960. In 2003, China reported the spread of the SARS-CoV to many countries. In 2012, Saudi Arabia reported infection and deaths from a CoV which was was named as MERS-CoV, stands for Middle East respiratory syndrome coronavirus. The novel 2019 CoV is named SARS-COV-2 because it has a genetic similarity and biochemical resemblance more to SARS-CoV.

The transmission and infection of CoVs have been shown to infect the cells of the respiratory mucosa; this can occur...
when virus particles are inhaled or come in a direct contact with a mucosal surface of the mouth, nose, or eyes. It can also transmit through a physical contact when someone touches the infected surface and then touches their nose, eyes, or mouth. Generally, viruses can also spread by the airborne route in small droplet nuclei that can remain suspended for long periods of time and inhaled. Respiratory viruses preferentially bind and infect ciliated or nonciliated epithelial cells of the respiratory epithelium Airways, which are pneumocytes lining the alveoli in the lungs and alveolar macrophages.4

The attachment receptor for SARS-CoV and SARS-CoV-2 is the human angiotensin-converting enzyme 2 (ACE2).5 After its attachment to the receptor, the virus is engulfed by the cell and the viral genome either DNA or RNA is uncoated to release the viral genetic material, which is RNA in case of SARS-CoV-2. The replication cycle of CoVs occurs entirely in the cytoplasm and involves the production of a series of subgenomic RNAs, which further makes proteins for virion assembly. Progeny virions are released from the infected cells into the surrounding cells and tissues in the respiratory tract, where they are shed by coughing and sneezing. During the incubation period, the virus attaches to and infects cells, replicates its genome, and spreads to infect adjacent cells.6 The incubation period for SARS-CoV-2 is found to be from 4.5 to 5.8 days, with an average of 5.1 days.7

From the earliest reports, ACE2 receptors have been shown to be present in many organs and tissues of human body. An immunohistochemistry analysis revealed that SARS-CoV was predominantly present in the lungs, trachea, and bronchi and was also detected in many other organs and tissues, such as the stomach, small intestine, distal convoluted renal tubule, sweat gland, parathyroid, pituitary, pancreas, adrenal, liver, and cerebrum.8 CoVs have also been detected in tissues such as endothelial cells of small and large arteries and veins, type I and type II alveolar epithelial cells in normal lungs, in the basal layer of the nonkeratinizing squamous epithelium of nasal and oral mucosa and the nasopharynx, basal cell layer of the epidermis extending to the basal cell layer of hair follicles, endothelial and smooth muscle cells of the brain, etc.9

Clinical features of COVID-19 ranging from an asymptomatic state to acute respiratory distress syndrome and multi-organ dysfunction. SARS-CoV-2 leads to chronic inflammation of the lungs, severe dyspnea, fever, dry cough, cyanosis, and complete lung failure in more vulnerable patients. The typical clinical features include fever, cough, sore throat, headache, fatigue, myalgia, and breathlessness. In some patients, the disease can progress to pneumonia, respiratory failure, and ultimately death. The disease progression is associated with an increase in inflammatory cytokines including IL2, IL6, IL7, IL10, GCSF, IP10, MCP1, MIP1A, and TNFα. The disease in neonates, infants, and children has been reported to be significantly milder than adults.10

A neuroinvasion mechanism by SARS-CoV-2 is proposed through the olfactory bulb and the olfactory nerve. The COVID-19 virus’s movement to the brain via the cribriform plate close to the olfactory bulb can be an additional pathway. From the olfactory bulb and the olfactory nerve, it would spread to various parts of the brain by a synapse-connected route and trans-synaptic transfer and infects the pre-Botzinger complex in the brainstem, the respiratory center of the brain that controls the lungs, shutting down breathing, and causing potential death, similar to what has been proposed by SARS-CoV-2.11 There are only a few case reports till the time which show SARS-CoV-2 in the cerebrospinal fluid (CSF) of patients; studies of acute SARS-CoV illness in the past have demonstrated the presence of the virus in CSF.12 In the past, autopsy findings of the SARS-CoV-infected patients have shown strong evidence of the SARS-CoV’s presence in the brain by electron microscopy, immunohistochemistry, and real-time reverse transcription-polymerase chain reaction (RT-PCR).13

Methods

This review’s inclusion criteria were as follows: all studies with any study design that reported the neurological features in a cohort of more than 50 patients with COVID-19 and published on or prior to August 1, 2020 were included. Two electronic databases, namely PubMed and Google Scholar, and one worldwide online search engine Google were searched for the concerned articles. The lists of references in the included studies were also screened for any relevant papers. In this review, we have excluded Chinese studies that do not have coauthors from other countries except the pioneer study by Mao et al., which has scored more than 1,000 citations as on August 1, 2020. Also, preprint platforms and their publications were not considered in this study.

This review analyzed 247 research and reviewed articles using the keywords neurological manifestations, neuroinvasion, neuroimaging, coronavirus, COVID-19, SARS-CoV-2, cohort, population, analysis in all possible combinations. The final list of included articles was generated on the basis of relevance to the topics covered in this review. After removal of duplicate, non-original articles and preprints, a total of 102 articles were used for an initial screening based on titles and abstracts. Out of 102 studies, 48 studies were selected for the full-text review. Finally, 5 reviews and 9 clinical studies were taken in the present study as they met the inclusion criteria (Figure 1).14–27

Results

The study find out that COVID-19 patients do have concurrent neurological manifestations that are subjected to further study. We collected 97 reviews through the search strategy described in this review and finally included 5 studies that could fit in
Table 1. Selected Review Reports of Neurological Manifestations Associated With COVID-19

| S. No. | Title                                                                 | Date of Publication | No. of Studies/ Patients | Conclusion From the Review                                                                 |
|--------|----------------------------------------------------------------------|---------------------|--------------------------|-------------------------------------------------------------------------------------------|
| 1      | Neurological manifestations of COVID-19: A systematic review and current update | May 10, 2020        | 31 studies               | Anosmia, headache seizures, stroke, and Guillain–Barré syndrome                           |
| 2      | A review of neurological complications of COVID-19                    | May 18, 2020        | 15 studies               | Headache, dizziness anosmia, ageusia, Miller Fisher syndrome, olfactory dysfunction, and encephalopathy |
| 3      | Neuropathogenesis and neurological manifestations of the coronaviruses in the age of coronavirus disease 2019: A review | May 29, 2020        | Not specified            | Anosmia, ageusia, headache, stroke, impairment of consciousness, seizures, and encephalopathy |
| 4      | Neurological and musculoskeletal features of COVID-19: A systematic review and meta-analysis | June 26, 2020       | 60 studies               | Anosmia, ageusia, myalgia, headache, back pain, and dizziness                             |
| 5      | Neurological associations of COVID-19                                 | July 02, 2020       | 901 patients             | Encephalopathy, encephalitis, Guillain–Barré syndrome, anosmia, ageusia, acute cerebrovascular disease, and stroke |
Table 2. Selected Clinical Studies of Cohort Showing Neurological Manifestations Associated With COVID-19

| S. No. | Author, Type of Study, and Country | No. of Neurologically Affected Patients | SARS-CoV-2 Diagnostic Test | Major Neurological Clinical Presentation | Brain Abnormalities Findings |
|--------|-----------------------------------|----------------------------------------|---------------------------|------------------------------------------|------------------------------|
| 1.     | Mao et al., retrospective study, China | 214 | RT-PCR positive | Dizziness, headache, hypogeusia, hyposmia, acute cerebrovascular diseases, impaired consciousness, and skeletal muscle injury | Not available |
| 2.     | Helms et al., observational study, France | 58 | RT-PCR positive | Agitation, confusion, dys-executive syndrome, and encephalopathy | MRI showed leptomeningeal enhancement, perfusion abnormalities, and cerebral ischemic stroke |
| 3.     | Varatharaj et al., UK-wide surveillance study, UK | 125 | RT-PCR positive, or anti-SARS-CoV-2 IgM, or IgG positive | Ischemic stroke, intracerebral hemorrhage, cerebral vasculitis, encephalopathy, encephalitis, Guillain–Barré syndrome and variants, neuropsychiatric (dementia-like) syndrome, psychiatric disorder, psychosis, dementia-like syndrome, and affective disorder | Not available |
| 4.     | Romero-Sánchez et al., ALBACOVID registry, retrospective, observational study, Spain | 841 | RT-PCR positive, or anti-SARS-CoV-2 IgM, or IgG positive | Myalgia, headache, dizziness, anosmia, dysgeusia, impaired consciousness, myopathy, dysautonomia, cerebrovascular diseases, seizures, movement disorders, encephalitis, Guillain–Barré syndrome, and optic neuritis | Electroencephalogram showed moderate encephalopathy in two patients, one patient showed MRI pattern resembling posterior reversible encephalopathy syndrome, one patient showed bilateral temporal hyperintensity in FLAIR sequences of brain MRI |
| 5.     | Benussi et al., retrospective study, Italy | 56 | RT-PCR positive, bronchoalveolar lavage | Ischemic attack, ischemic stroke, hemorrhagic stroke, and epilepsy | Not available |
| 6.     | Lu et al., prospective study, China | 60 | RT-PCR positive | Mood change, fatigue, headache, vision change, myalgia, impaired mobility, memory loss, taste loss, limb numbness, tremor, smell loss, and hearing loss | Diffusion tensor imaging and 3D high-resolution T1 weighted image showed significantly higher bilateral gray matter volumes (GMVs) in olfactory cortices, hippocampi, insulas, left Rolandic operculum, left Heschl’s gyrus, and right cingulated gyrus and a general decline of MD, AD, RD accompanied with an increase of FA in white matter, especially AD in the right CR, EC and SFF and MD in SFF |
| 7.     | Yan et al., cross-sectional study, USA | 59 | RT-PCR positive | Anosmia and ageusia | Not available |
| 8.     | Lechien et al., European study | 417 | RT-PCR positive | Olfactory dysfunction, anosmia, hyposmia, and gustatory disorders | Not available |
| 9.     | Kandemirli et al., observational study, Turkey | 749 | Not specified | Not available | Cortical, subcortical, and deep white matter FLAIR signal abnormality |
Mao and coworkers reported that 36.4% of the 214 patients had neurological symptoms. 24.8% of these patients exhibited central nervous system (CNS) symptoms, the most common of which were dizziness (16.8%) and headache (13.1%) and less common were the alteration of mental status, acute cerebrovascular accident (CVA), ataxia, and seizures. 19

Helms et al. reported neurological complications in an observational case series of 58 patients admitted to the intensive care unit (ICU) for acute respiratory distress syndrome, in Strasbourg, France. Neurological findings were seen in 14% of patients at admission and 69% of cases were seen when they were weaned off sedation and paralytics. The most frequently observed symptoms were confusion (65%), agitation (69%), upper motor neuron syndrome signs like hyperreflexia with clonus and positive Babinski’s sign (69%) during the ICU stay, and a dysexcutive syndrome (33%) after discharge. Magnetic resonance imaging (MRI) of the brain in patients who developed unexplained encephalopathic features revealed leptomeningeal enhancement (62%), perfusion abnormalities (100%), and ischemic CVA (23%). 20

In one UK-wide national surveillance study of 125 patients with COVID-19 and neurological or psychiatric disease reported over three weeks showed that 39 (31%) patients had altered mental status, which included 16 (13%) with encephalopathy [of whom seven (6%) had encephalitis], and 23 (18%) with a neuropsychiatric diagnosis, including 10 (8%) with psychosis, 6 (5%) with neurocognitive (dementia-like) syndrome, and 4 (3%) with an affective disorder. Notably, 77 (62%) patients had a cerebrovascular event: 57 (46%) ischemic strokes, 9 (7%) intracerebral hemorrhages, 1 (<1%) had CNS vasculitis, and 10 (8%) presented other cerebrovascular events. 21

Romero-Sánchez et al. reported that in 841 patients hospitalized with COVID-19 in Spain, myalgia (17.2%), headache (14.1%), and dizziness (6.1%) were present mostly in the early stages of infection. Anosmia (4.9%) and dysgeusia (6.2%) were the next most common symptoms. The other symptoms reported were disorders of consciousness (19.6%), myopathy (3.1%), dysautonomia (2.5%), cerebrovascular diseases (1.7%), seizures (0.7%), movement disorders (0.7%), encephalitis (n = 1), Guillain–Barre syndrome (n = 1), and optic neuritis (n = 1). Neurological complications were the main cause of death in 4.1% of all deceased study subjects. 22

Benussi et al. from Italy observed a significant increase in cerebrovascular disease rates in the COVID-19 group (n = 43, 76.8% vs. n = 68, 58.1%, P = .02), with a similar distribution between transient ischemic attack (n = 5, 11.6% vs. n = 8, 11.9%), ischemic stroke (n = 35, 81.4% vs. n = 50, 74.6%), and hemorrhagic stroke (n = 3, 7.0% vs. n = 9, 13.4%) within groups. 23

Smell and taste loss showed the largest magnitudes of association with COVID-19 positivity reported in 68% (40/59) and 71% (42/59) of COVID-19-positive subjects by Yan et al. Self-reported symptoms associated with COVID-19 positivity in order of descending frequency included fatigue (81%), ageusia (71%), fever (70%), anosmia (68%), myalgia or arthralgia (63%), diarrhea (48%), and nausea (27%). 24

A multicenter European study by Lechien et al. showed that 85.6% and 88.8% of a total of 357 patients reported olfactory and gustatory dysfunctions, respectively, with the olfactory dysfunction emerging before other symptoms in 11.8% cases. 284 (79.6%) patients were anosmic and 73 (20.4%) were hyposmic. Phantosmia and parosmia were reported in 12.6% and 32.4% of patients, respectively. 25

Structural changes in the brain can provide excellent inputs to understand the effect of COVID-19 on the brain and nervous system. Lu et al. reported cerebral microstructural changes in COVID-19 patients. Neurological symptoms were present in 55% of COVID-19 patients. They further found that the recovered COVID-19 patients were more likely to have enlarged olfactory cortices, hippocampi, insulas, Heschl’s gyrus, Rolandic operculum and cingulate gyrus, and a general decline of mean diffusivity (MD), axial diffusivity (AD), radial diffusivity (RD) accompanied by an increase of fractional anisotropy (FA) in white matter (WM), especially AD in the right coronal radiata (CR), external capsule (EC) and superior frontal-occipital fasciculus (SFF), and MD in SFF as compared to non-COVID-19 volunteers. Global gray matter volume (GMV), GMVs in the left Rolandic operculum, right cingulate, bilateral hippocampi, left Heschl’s gyrus, and global MD of WM were found to correlate with memory loss. GMVs in the right cingulate gyrus and left hippocampus were related to smell loss. 27

Kandemirli et al. showed that COVID-19 patients had acute findings in brain MRI, which include a cortical, subcortical, and deep white matter fluid-attenuated inversion recovery (WM FLAIR) signal abnormality. Abnormalities were also present in the frontal lobe, parietal lobe, occipital lobe, temporal lobe, insular cortex, and cingulated gyrus. 27

We have also analyzed neuropsychiatric conditions in the COVID-19 pandemic and found that many conditions like anxiety, amnesia, hallucinations, depression, sleep disorder, delirium, mood swings, and suicidal thoughts were also present in the general population because of increased psychosocial stress, psychotropic drugs usage, etc., during the pandemic. 28 Thus, neurological and neuropsychiatric manifestations can become a more pressing concern as the pandemic spreads and has long-term effects on the general population.

Discussion

There are only a few studies that have shown the relation between the SARS-CoV-2 infection and neurological complications in COVID-19 patient cohorts. The human brain has been reported to express ACE2 receptors that have been detected in glial cells and neurons in mice, which makes them a potential target of SARS-CoV-2. Neurologists categorized neurological manifestations into nonspecific
symptoms (headache, dizziness, or myalgia), neuropsychiatric disorders (insomnia, depression, anxiety, or psychosis), CNS disorders (direct viral infection, encephalitis, disorders of consciousness, seizures, and stroke), peripheral nervous system disorders (cranial neuropathies, anosmia/dysgeusia, and peripheral neuropathy), myopathy, demyelinating events, and cerebrovascular manifestations.

This study is based on the findings of neurological symptoms in the COVID-19 population, which further discusses present and future implications in the COVID-19 management. By reviewing cohort-based studies, we have analyzed common as well as other neurological symptoms that need attention in health care settings. These findings also have relevance for follow-up studies as many of the patients showed up psychiatric problems that do not involve any underlying pathology but were occurred because of a psychosocial effect on the brain and behavior. It has been established that CoVs have a potential to reach brain receptors through the ACE2 receptor which is present in many tissues of the brain and is proposed through two routes, i.e., olfactory bulb and cribriform plate.

First, we analyzed the review papers that reported neurological symptoms in COVID-19 patients. Based on the inclusion criteria, five studies came out to be most appropriate, which show that neurological symptoms such as anosmia and ageusia were the most common and were noted in all five studies (5/5). It was followed by headache (4/5), stroke (3/5), encephalopathy (3/5), seizures (2/5), encephalitis (1/5), Guillain–Barré syndrome (1/5), and Miller Fisher syndrome (1/5). Other less common neurological symptoms that were reported in review studies were impaired consciousness, acute cerebrovascular disease, myalgia, back pain, and dizziness.

To further study the prevalence of each neurological symptom, we analyzed clinical research studies which have recruited a large number of COVID-19 patients. We analyzed studies from different countries across the globe to see if these symptoms are emerging from all over or have geographical restrictions, because lockdown conditions in different countries can give rise to different neurological manifestations. A more detailed examination of symptoms revealed that apart from the findings from review studies there are many more neurological symptoms that are emerging out after the critical examination of patients. These symptoms are hearing loss, skeletal muscle injury, agitation, confusion, dysexecutive syndrome, intracerebral hemorrhage, cerebral vasculitis, psychosis, myopathy, dysautonomia, optic neuritis, epilepsy, mood change, fatigue, memory loss, limb numbness, tremor, etc. In some cases, these findings were very well substantiated by examining structural changes in the brain by performing brain MRI, diffusion tensor imaging, and 3D high-resolution T1 weighted image, which shows that these kinds of studies should be performed in future to see the exact changes in the brain after the SARS-CoV-2 infection. Restrictions imposed during pandemic like lockdown have shown number of psychosocial effects in the community. Symptoms such as anxiety, amnesia, hallucinations, depression, sleep disorder, delirium, mood swings, and suicidal thoughts were observed in COVID-19 patients as well as in the general population.

Conclusion

Neurological manifestations of COVID-19 have not been studied in detail yet. It is possible that patients having severe illness, developed CNS and neurological manifestations. The most commonly reported neurological symptoms such as anosmia, gustatory impairment along with altered mental status should not be ignored and the patients in these cases must be tested for COVID-19. Based on the available pieces of evidence, it is suggested that health care units taking care of infected patients must now include neurologists to gain more perspective into the nature of the infections, which can be neurological. More autopsies on brains of the COVID-19 patients with neurological symptoms need to be performed to establish the neuroinfection track of the disease. A through neurological assessment should be performed to note neurological symptoms (e.g., headache, dizziness, etc.) and signs (e.g., change in mental status, meningeal signs, etc.), detailed clinical, neurological, and electrophysiological investigations (e.g., electroencephalogram) of the patients particularly those with a change in mental status should be followed. Attempts to isolate SARS-CoV-2 from CSF may clarify the roles played by this virus in causing neurological manifestations. Medical imaging and neuropathology will undoubtedly play an essential role in detecting abnormalities in the olfactory bulb, cranial nerves, and brains of COVID-19 patients.

Author Contribution

Dr Rachna Agarwal designed the study and approved the final manuscript. Kamal Pratap Singh performed the literature analysis and wrote the manuscript.

Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Ethical Statement

No ethical consent was required from the Institutional Ethics Committee.

Funding

The authors received no financial support for the research, authorship, and/or publication of this article.
References

1. Schalk A., An apparently new respiratory disease of baby chicks. J Am Vet Med Assoc 1931; 78: 413–423.
2. Estola T., Coronaviruses, a new group of animal RNA viruses. Avian Dis 1970 May; 14(2): 330–336.
3. Tyrrell D, Almeida J, Cunningham C, et al. Coronaviridae. Intervirology 1975; 5: 76.
4. Subbarao K, and Mahanty S., Respiratory virus infections: Understanding COVID-19. Immunity 2020 Jun 16; 52(6): 905–909.
5. Shang J, Ye G, Shi K, et al. Structural basis of receptor recognition by SARS-CoV-2. Nature 2020; 581: 221–224.
6. Fehr AR, Perlman S., Coronaviruses: An overview of their replication and pathogenesis. Methods Mol Biol 2015; 1282: 1–23.
7. Lauer SA, Grantz KH, Bi Q, et al. The incubation period of coronavirus disease 2019 (COVID-19) from publicly reported confirmed cases: Estimation and application. Ann Intern Med 2020; 172: 577–582.
8. Ding Y, He L, Zhang Q, et al. Organ distribution of severe acute respiratory syndrome (SARS) associated coronavirus (SARS-CoV) in SARS patients: Implications for pathogenesis and virus transmission pathways. J Pathol: J Pathol Soc Great Br Ireland 2004; 203: 622–630.
9. Hamming I, Timens W, Bulthuis M, et al. Tissue distribution of ACE2 protein, the functional receptor for SARS coronavirus. A first step in understanding SARS pathogenesis. J Pathol: A J Pathol Soc Great Br Ireland 2004; 203: 631–637.
10. Singh T., A review of coronavirus disease-2019 (COVID-19). Indian J Pediatr 2020 Apr; 87(4): 281–286.
11. Baig AM, Khaleeq A, Ali U, et al. Evidence of the COVID-19 virus targeting the CNS: Tissue distribution, host–virus interaction, and proposed neurotropic mechanisms. ACS Chem Neurosci 2020; 11: 995–998.
12. K-K Lau, W-C Yu, C-M Chu, et al. Possible central nervous system infection by SARS coronavirus. Emerg Infect Dis 2004; 10: 342.
13. Dinakaran D, Manjunatha N, Kumar CN, et al. Neuropsychiatric aspects of COVID-19 pandemic: A selective review. Asian J Psychiatr 2020 Oct; 53: 102188.