Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Review article

Neurological manifestations and complications of COVID-19: A literature review

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ABSTRACT

The Coronavirus disease due to SARS-CoV-2 emerged in Wuhan city, China in December 2019 and rapidly spread to more than 200 countries as a global health pandemic. There are more than 3.5 million confirmed cases and around 165,000 to 243,000 fatalities. The primary manifestation is respiratory and cardiac but neurological features are also being reported in the literature as case reports and case series. The most common reported symptoms to include headache and dizziness followed by encephalopathy and delirium. Among the complications noted are Cerebrovascular accident, Guillian barre syndrome, acute transverse myelitis, and acute encephalitis. The most common peripheral manifestation was hyposmia. It is further noted that sometimes the neurological manifestations can precede the typical features like fever and cough and later on typical manifestations develop in these patients. Hence a high index of suspicion is required for timely diagnosis and isolation of cases to prevent the spread in neurology wards. We present a narrative review of the neurological manifestations and complications of COVID-19. Our aim is to update the neurologists and physicians working with suspected cases of COVID-19 about the possible neurological presentations and the probable neurological complications resulting from this novel virus infection.

1. Introduction

The Novel Coronavirus (COVID-19) outbreak originated from the Wuhan city, China in December 2019 [1,2] Chinese authorities reported unusual cases of pneumonia with an undetermined etiology [3]. Initially all cases were clustered to the Huanan seafood wholesale market. World Health Organization (WHO) declared it a pandemic on 11 March 2020 [4]. As of 19th April 2020, there are more than 2.3 million confirmed case of COVID-19 with 162,000 fatalities in the world [5].

COVID-19 has generated a great interest among physicians, scientists, and researchers all around the globe [6]. The amount of research and number of articles being published on COVID-19 is unprecedented. It has been estimated that hundreds of manuscripts have been published on this topic since the start of the year [7]. Data on different aspects of the disease manifestations, pathology, transmission, prevention, and management strategies has started emerging [8,9,10] Although COVID-19 preferentially affects the respiratory and cardiovascular system, *several patients of COVID-19* are also likely to have neurological symptoms (such as headache, dizziness, hypogeusia, and neuralgia) and complications including encephalopathy, acute cerebrovascular diseases, impaired consciousness and skeletal muscular injury [11,12].

We present a narrative review of the neurological manifestations and complications of COVID-19. Our aim is to update the neurologists and physicians working with suspected cases of COVID-19 about the possible neurological presentations and the probable neurological complications resulting from this novel virus infection.

We searched Medline, PubMed Central and Google Scholar using keywords " COVID-19", "Coronavirus", "pandemic", "SARS-COV-2", "neurology", "neurological", "complications" and "manifestations". Search was limited only to English language manuscripts with no time limit. The literature search was last done on 11th April 2020. It is important to note that new data is being shared regularly and so far, it consists mostly of pre-prints, case reports, small case series, and part of an article describing clinical features of COVID-19. Most of the data on COVID-19 at present is being published from China [13]. At the time of writing this article we were able to locate only 2 full text articles in English biomedical literature specifically describing the neurological manifestations and complications in COVID-19 in detail.

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2. Mechanism of CNS invasion

There is not enough experimental data available for COVID-19, but it is considered a mutation of Severe Acute Respiratory Syndrome **Virus** and Middle East Respiratory syndrome Virus [14]. Therefore, it is expected that it will behave in a similar manner [15]. Corona viruses are not primarily neurotropic virus and their primary target is respiratory epithelium. The target receptor for attachment to cell and subsequent internalization is through the angiotensin converting enzyme-2 receptor (ACE 2). After entry into the cell the virus RNA is released in the cytoplasm subsequently translated and replicated, after formation of envelope protein and incorporation of RNA into it the virus is released in the circulation [16].

ACE 2 receptors are also found in glial cells in brain and spinal neurons. Hence it can attach, multiply and damage the neuronal tissue. There is evidence from the animal experiments in mice that coronavirus enters the brain through a retrograde transfer via the olfactory epithelium or through the cribriform bone and reaches the brain in seven days' time. Secondly, during the viremia phase of illness, disruption of blood brain barrier causes the virus to enter the brain directly. Another postulated mechanism is the invasion of peripheral nerve terminals by CoV which then gains entry to the CNS through the synapse connected route. Since COVID-19 has similarities with Severe Acute Respiratory Syndrome (SARS Cov), therefore it can be presumed that it also follows the same pathways for CNS invasion as discussed above. The detailed discussion of host and virus interaction is beyond the scope of this article, and has been published elsewhere [15,16].

2.1. Neuropathological mechanism of CNS damage

COVID-19 results in neurological damage likely by two mechanisms; hypoxic brain injury and an immune mediated damage to the CNS.

2.1.1. Hypoxic brain injury

Severe pneumonia can result in systemic hypoxia leading to brain damage. The contributory factors include peripheral vasodilatation, hypercarbia, hypoxia and anaerobic metabolism with accumulation of toxic compounds. These can result in neuronal swelling and brain edema which ultimately results in neurological damage [9].

2.1.2. Immune mediated injury

Immune mediated injury is mainly due to the cytokine storms with increased levels of inflammatory cytokines and activation of T lymphocytes, macrophages, and endothelial cells. Further release of Interleukins 6 causes vascular leakage, activation of complement and coagulation cascade, disseminated intravascular coagulation and end organ damage [17,18].

3. Neurological manifestations of COVID-19

The important neurological manifestations and complications of COVID-19 reported in literature so far are summarized in Table 1. There are 2 case series specifically describing neurological manifestations and complications in COVID-19 patients. The first is a retrospective case series on neurological manifestation from China by Mao et al. [11] They reported the patients in two groups. The severely ill group had 88 (41.1%) patients while there were 126 (58.9%) patients in the non-severely ill group. Patients in the severely ill group were significantly older (58.2 ± 15 years Vs. 48. 9 ± 14.7 years) with more co-morbid conditions especially hypertension (32 [36.4%] Vs. 19 [15.1%],). Surprisingly the severely ill group had less typical symptoms of coronavirus like fever (40 [45.5%] Vs. 92 [73%],) and dry cough (30 [34.1%] Vs. 77 [61.1%],). However, nervous system symptoms were significantly more common in severe cases as compared with non-severe cases (40 [45.5%] Vs. 38 [30.2%],). The most common CNS symptoms reported were dizziness (36 [16.8%] and headache (28 [13.1%]).

Table 1
Comparison of Neurological complications and manifestations between the severely ill Chinese and French patient series.

Variable	Mao et al. [11]	Helms et al. [12]
Study design	Retrospective Chart review	Observational study
Total Number of cases	214	58
Number of seriously ill patients	88	58
Median Age (Years)	58.7	63
Neurological Involvement	45.5%	84%
Dizziness	19.3%	NR
Headache	17.1%	NR
Impaired consciousness	14.8%	NR
Hypogeusia	5.6%	NR
Hyposmia	5.1%	NR
Skeletal muscle injury	19.3%	NR
Simplified Acute Physiology Score II	NR	52
Agitation	NR	40 (69%)
Delirium as documented by CAM-ICU	NR	26 (65%)
Corticospinal tract signs	NR	39 (67%)
Dysexecutive syndrome at discharge	NR	14 (36%)
Ischemic stroke	5 (5.7%)	3/13 (23%)
Hemorrhagic Stroke	1 (1.13)	Nil
Leptomeningeal enhancement on MRI	NR	8/13 (62)
EEG	NR	1(8) diffuse bifrontal slowing

Foot Notes. CAM-ICU; Confusion assessment method in Intensive care unit, EEG; electroencephalogram, MRI; Magnetic resonance imaging, NR; Not reported.

The second article is a prospective case series of 58 patients from France [12]. The median age of patients was 63 years and neurological complications were seen in a higher percentage 49/58 (84%). As assessed by confusion Assessment method for intensive care unit CAM-ICU scale, agitation was the most common symptoms 40/58 (69%) followed by confusion 26/40 (65%).Corticospinal tract signs were present in in 39/58 (67%)and a dysexecutive syndrome at the time of discharge was noted in14/39 (36%). Table 1 shows the comparison between the two study cohorts.

The neurological manifestations and complications of COVID-19 can be divided into central and peripheral as discussed below Table 2.

Table 2
Neurological complications and manifestations of COVID-19.

Site	Manifestations and Complications
Central Nervous System	Dizziness Headache Acute cerebrovascular disease Impaired consciousness Transverse myelitis Acute hemorrhagic necrotizing encephalopathy Encephalopathy Encephalitis Epilepsy Ataxia
Peripheral Nervous System	Hypogeusia Hyposmia, Neuralgia Guillian Barre syndrome Skeletal muscle injury

3.1. Central nervous system manifestations

3.1.1. Encephalopathy

Mao et al reported headache and encephalopathy in 40% of patients in their cohort but the details and the diagnostic criteria used was not described [11]. Filatove et al reported a case of a 74-year-old male with past medical history of atrial fibrillation, stroke, Parkinson disease, chronic obstructive pulmonary disease, and recent cellulitis, who presented to the emergency department with fever and cough [19]. Initial diagnostic work up did not suggest any serious issue and he was discharged to home. He reported back with worsening symptoms, including headache, altered mental status, fever, and cough. Chest X ray was suggestive of pneumonia, while CT scan brain was unremarkable except for signs of previous stroke. PCR assay of CSF was negative for infection. He tested positive for COVID-19 and was intubated after developing respiratory failure. He was started on hydroxychloroquine, lopinavir/ritonavir, and was continued on broad-spectrum antibiotics.

Chen et al. in a retrospective study of the clinical characteristics of 113 COVID-19 patients from China, documented hypoxic encephalopathy in 20 patients [20]. The incidence was significantly lower in the patients who had recovered.

3.1.2. Acute hemorrhagic necrotizing encephalopathy (ANE)

Poyiadji and colleagues reported the first case of COVID-19–associated acute hemorrhagic necrotizing encephalopathy (ANE) from USA [21]. A female patient in her late fifties presented with a 3-day history of cough, fever, and altered mental status. Polymerase chain reaction (PCR) assay was positive for COVID-19 and negative for Herpes Simplex Virus 1 and 2, West Nile and Varicella Zoster Virus. Non contrast head CT images demonstrated symmetric hypoattenuation within the bilateral medial thalami with a normal CT angiogram and CT venogram. MRI brain demonstrated hemorrhagic rim enhancing lesions within the bilateral thalami, medial temporal lobes, and sub insular regions. She was started on intravenous Immunoglobulin (IVIG), but the outcome was not mentioned. ANE is a rare complication of viral infections like influenza. The proposed mechanism is likely due to cytokine storm which results in disruption of blood brain barrier and damage to the brain parenchyma.

3.1.3. Acute myelitis

Kang Zhao et al reported acute myelitis in a 66-year-old male form Wuhan city who presented with fever and body aches [22]. During the admission he developed acute flaccid paralysis of bilateral lower limbs, sensory level at T-10 with urinary and bowel incontinence. CT scan chest confirmed patchy pneumonia and PCR for nasopharyngeal secretion was positive for COVID-19 infection. His serology for all other organism was negative.

He was treated empirically with IVIG, steroids, antibiotics and antiviral. The response to treatment was good and he was discharged to an isolation facility for further rehabilitation. The authors attributed acute myelitis to the cytokine storm and overactive inflammatory response as evident by high levels of serum ferritin, C-reactive protein, Serum Amyloid-A and Interleukin-6 levels. A major limitation of this case report is the lack of CSF PCR for coronavirus and MRI imaging of spine due to epidemic in Wuhan city.

3.1.4. Cerebrovascular accident

Sharifi et al from Iran reported case of intracranial bleed resulting in CVA in a 79 Years old COVID-19 positive male [23]. He was admitted in the emergency in a semi-conscious state (Glasgow Coma Scale 7/15) with history of fever and cough. On examination there was, bilateral extensor planter response with coarse crepitation in left lower zones. PCR assay from nasopharyngeal secretion was positive for COVID-19. CT scan chest showed ground glass opacity suggestive of viral pneumonia. CT scan brain revealed a massive bleed within the right hemisphere with intraventricular and subarachnoid extension. This gentleman was neither a known hypertensive nor on any anticoagulants that could have caused this event. The platelets and PT/INR on admission were normal. The authors postulated that probably dysregulation in the ACE 2 receptors lead to cerebral auto regulation, sympatho-adreanl system and cerebral blood flow could have resulted in the bleed. Another aspect that is difficult to explain is the near normal blood pressure in this case at the time of admission.

Mao and colleagues reported six case of CVA in their cohort of 214 [11]. There were five ischemic and one case of hemorrhagic stroke. The French cohort had three cases of ischemic strokes which were detected on neuroimaging when the patients underwent imaging for encephlaophathy [12]. The patients did not have focal neurological signs. Probably the symptoms were masked due to presence of encephalopathy, but it highlights the importance of neuroimaging in evaluation of such cases. However more evidence is needed to establish a causal relationship between stroke and COVID-19.

3.1.5. Encephalitis

Moriguchi et all reported first confirmed case of COVID-19 associated viral encephalitis from Japan [24]. A 24 Years old man presented with fever followed by seizure and unconsciousness. He had neck stiffness and underwent CT scan brain which was normal. There was patchy pneumonia on CT chest. PCR assay from nasopharyngeal swab was negative but CSF sample was positive for COVID-19.The Diffusion weighted Images (DWI) showed hyperintensity along the wall of inferior horn of right lateral Ventricle. Fluid-attenuated inversion recovery (FLAIR) images showed hyperintense signal changes in the right mesial temporal lobe and hippocampus with slight hippocampal atrophy mainly on right mesial lobe and hippocampus. There was no post Contrast enhancement. The authors concluded that imaging findings were suggestive of right lateral ventriculitis and encephalitis. This case and presentation should alert clinicians regarding the neuroinvasive potential of COVID-19 and encephalitis like presentation.

3.1.6. Headaches and dizziness

Headaches and dizziness are a nonspecific and minor symptoms of many diseases. They have been reported as minor symptoms associated with presentation of COVID-19 in different reports. The incidence rages from 3 to 12.1% [25,26,27]. The detailed mechanism and pathophysiology has not been discussed in any of these reports

3.2. Peripheral Nervous system manifestations and complications

3.2.1. Anosmia and chemosensory dysfunction

Yan et al from USA, documented chemosensory dysfunction in 59 COVID-19 positive and 203 COVID-19 negative patients from a single center using an internet based cross sectional survey [28]. They demonstrated that the smell and taste dysfunction was higher in the COVID-19 positive cases as compared to the negative cases. (smell loss: 68% Vs. 16 % and taste loss: 71% Vs. 17%). Most of the patients in this study were ambulatory, did not need hospitalization and none required mechanical ventilation. They theorized that probably in ambulatory COVID-19 patients virus spreads via the nasal route as compared to the seriously ill patients in which the spread is most likely pulmonary. Bagheri et al reported results of a large Iranian cohort of 10,069 patients by employing an online questionnaire-based survey [29]. Participants were cases with problems in decreased sense of smell recently (within the last 04 weeks of onset of COVID-19 outbreak in Iran). Anosmia and hyposmia was reported by 48.23% of the respondents

while 83.38% also had a decreased taste sensation. The onset of anosmia was sudden in 76.24%. Other clinical features reported by the participants were flu or cold symptoms before anosmia (75.5%), headaches (48.6%), nasal stiffness (43.7%) and fever (37.3%). In contrast the study by Mao et al. in their cohort of 214 Chinese patients reported impairment of taste in 12 (5.6%) and impairment of smell in 11 (5.1%) patients. Anosmia and taste dysfunction were not reported in the French cohort of COVID-19 patients.

3.2.2. Guillain barre syndrome (GBS)

So far eight cases of COVID-19 associated GBS have been reported from China, Iran and Italy. Zhao et al reported the first case of GBS in a 61 years old female who had travelled to Wuhan City, China [30]. She presented with acute weakness in both legs and severe fatigue, progressing within 1 day. Nerve Conduction Studies (NCS) and Electromyography (EMG) were suggestive of demyelinating polyneuropathy. She was treated with IVIG and later on developed respiratory symptoms. She tested positive for COVID-19. She infected two of her relatives and eight other people including two neurologist and six nurses who were isolated but were found negative for COVID-19. The author concluded that based on the travel history, lymphopenia, and thrombocytopenia at the time of admission are consistent with a Para-infectious pattern of GBS due to COVID-19. She made a good motor recovery after isolation and administration of anti-virals.

Sedaghat et al reported a 61 -Years old male with diabetes from Iran [31]. He had cough, fever and sometimes dyspnea two weeks before presenting with ascending paralysis leading to quadriplegia and bilateral facial paralysis. NCS/EMG was suggestive of acute motor sensoryaxonal neuropathy. He was managed with IVIG. Authors have suggested that GBS should be considered as a neurological complication of COVID-19 since respiratory involvement is common in COVID-19 and can be a risk factor for development of GBS. Virani and colleagues reported GBS in a 54-Years male from USA [32]. He presented with rapidly progressing ascending paralysis leading to respiratory difficulty. There was no bladder or bowel dysfunction. Reflexes were absent and MRI spine was normal. He had history of diarrhea preceding the acute attack of weakness. He tested positive for COVID-19. He was managed with IVIG and anti-malarial. He responded well and was weaned off from the ventilator. He was discharged to a rehabilitation facility for physical therapy.

Toscano et al reported five patients with GBS from Northern Italy [33]. Lower-limb weakness and paresthesia were the main presenting features in four patients, followed by facial weakness, ataxia, and paresthesia in one patient. Four had positive PCR from the nasopharyngeal swab on initial visit and fifth one was initially negative but later turned positive. On NCS/EMG 02 patients had features of demyelinating polyneuropathy while three had axonal polyneuropathy. All the patients were treated with IVIG. It was repeated in 02 patients and one patient had plasma exchange. After one week, only one patient was able to ambulate independently and discharged from the hospital. Further large scale studies are required to prove this causal relationship between COVID-19 and GBS.

3.2.3. Skeletal muscle damage

Mao et al reported skeletal muscle injury in 17 [19.3%] patients in the severely ill and 6 [4.8%] patients in the non-severe group [11]. They defined skeletal muscle injury as patient having myalgia and elevated serum creatine kinase level above 200 U/L. They concluded that it was not clear whether this was due to the direct effect of virus on muscle tissue. The other possible mechanism proposed was the infection-mediated immune response that causing elevated pro-inflammatory cytokines in serum resulting in skeletal muscle damage. However, it is important to note that patients in the severely ill group in addition to raised muscle enzymes, also had elevated liver enzymes and deranged renal functions which could have contributed to the this clinical picture. Moreover, no specific diagnostic workup for confirmation like NCS/EMG or muscle histopathology was performed. Therefore, it is difficult to exclude that these patients might be having critical illness myopathy and neuropathy in addition to skeletal muscle damage.

3.2.4. Other manifestations

Mao et al also reported neuralgia in five patients and epilepsy and ataxia in one each, but further details were not mentioned [11].

4. Conclusion

COVID-19 primarily affects the respiratory and cardiovascular system. However, neurological involvement is not uncommon and can result in serious complications if not detected and managed early. These complications are mostly seen in severely ill patients and in some cases can even precede the respiratory symptoms or many be the only symptoms in COVID-19 patients. Therefore, a high index of suspicion is required while dealing with such cases for prompt treatment and prevention. It is also important to systematically collect data on the short and long term neurological complications from different parts of the world and to document the functional outcomes after these complications.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jocn.2020.05.017.

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