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.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.
Neuropsychiatric manifestations of COVID-19 and possible pathogenic mechanisms: Insights from other coronaviruses

Debanjan Banerjee *, Biju Viswanath

Department of Psychiatry, National Institute of Mental Health and Neurosciences (NIMHANS), Bengaluru, India

ARTICLE INFO

Keywords:
COVID-19
Coronavirus
Neuropsychiatric
Pathogenesis
Sequelae
Review

ABSTRACT

Coronavirus disease 2019 (COVID-19) pandemic caused by SARS-CoV-2 has emerged as a global public health threat. Though the fear, anxiety, and stress related to COVID-19 have been studied in depth, the direct effects of SARS-CoV-2 on the central nervous system (CNS) remain elusive. Research related to the earlier coronavirus (CoV) outbreaks (like Severe Acute Respiratory Syndrome, SARS and Middle East Respiratory Syndrome, MERS) shows the neurotropic nature of CoV and the plethora of neuropsychiatric effects that it can cause. Though the current health priorities in managing COVID-19 remain restricted to containment and targeting pulmonary symptoms, the potential acute and long-term neuropsychiatric sequelae of the infection can increase morbidity and worsen the quality of life. Emerging evidence shows neural spread of the novel coronavirus. Delirium, encephalopathy, olfactory disturbances, acute behavioral changes, headache and cerebrovascular accidents are its common neuropsychiatric complications. These are directly related to increase in peripheral immunological markers, severity of infection and case fatality rate. This narrative review synthesizes available evidence related to the neuropsychiatric manifestations of COVID-19. Also, as SARS-CoV-2 shares structural and functional similarities with its earlier congeners, this article proposes possible long-term neuropsychological sequelae and pathogenic mechanisms for the same, based on research in the other coronavirus outbreaks.

1. Introduction

The world is witnessing a new public health threat since the beginning of this year. Coronavirus disease 2019 (COVID-19), caused by the novel Coronavirus SARS-CoV-2, originated in Wuhan, China towards the end of last year and was declared by the World Health Organization (WHO) to be a ‘Public Health Emergency of International Concern’ (PHEIC) within a month of its emergence. Subsequently, it turned into an epidemic six weeks later (Sohrabi et al., 2020). With more than six million affected and nearly four lakhs succumbing to the infection, WHO has termed it the largest infectious outbreak that the modern world has ever seen (WHO COVID-19 Situation Report, as on 15 June 2020). Fear, health anxiety, apprehension, uncertainty, loneliness and mass-hysteria are the common offshoots since COVID-19 began (Banerjee, 2020), as billions are quarantined at their homes, borders sealed and economies crashing down. Various studies have already mentioned a direct psychological impact on the vulnerable populations like elderly, migrants, homeless and also the frontline workers including the health care staff (Chen et al., 2020c; Yang et al., 2020b). High workload, absenteeism, burnout and guilt contribute to these outcomes in such individuals. Incidence of depression, anxiety and suicidality have been reported across many countries, compounded by the effects of the lockdown (Li and Ge et al., 2020). Most studies from China, one of the first hit countries in this outbreak, have stressed on the importance of integrating online and community-based mental health services into the public health infrastructure as an attempt to combat the aftermath of this infection (Duan and Zhu, 2020; Liu et al., 2020b).

Even though the social and psychological effects have been studied to some extent, the direct effects of the SARS-CoV-2 on the central nervous system and role of psychoneuroimmunity are largely unknown. It is a well-established fact that immunity plays a major role in the genesis and severity of COVID-19. Supporting evidence includes the inverse relationship between lymphocyte counts, C-reactive protein (CRP) and Erythrocyte Sedimentation rate (ESR) levels and the severity of infection. Mortality has been associated with poor antibody titer in response to the infection (Ruan et al., 2020). Neuro-invasive properties of the virus have been linked to respiratory failure and fatality rate (Li and Bai et al., 2020). Also, convalescent plasma exchange is emerging as...
a promising therapy (Keith et al., 2020). Keeping in mind that the earlier outbreaks caused by different types of Coronavirus (CoV) (Severe Acute Respiratory Syndrome, SARS and Middle East Respiratory Syndrome, MERS) have produced varied neuropsychiatric manifestations, it is logical to assume that COVID-19 carries the same risk too. They mostly include acute meningoencephalitis, anosmia, manic-depressive disorders, demyelination, agitation and delirium (Honigsbaum, 2013). Similar findings have been found in the H1N1 influenza outbreaks of Europe, Zika outbreak in Brazil and earlier the Nipah infection in Singapore. In addition, complex and generalized seizures, encephalopathy, Guillain-Barre syndrome (GBS) and peripheral neuropathies have been reported in these viral infections (BY Ng et al., 2004; e Silva et al., 2016).

The neurotropism of SARS-CoV-2 is still under debate. However, animal studies using nasal inoculation has clearly shown the transcripnbial spread of the virus, with proliferation in the oligodendrocytes and endothelial cells. Post-mortem sections of pyriform cortex, basal ganglia and hypothalamus have shown the viral particles (Chan et al., 2020). Clinically, the neuropsychiatric manifestations of COVID-19 can be either acute or chronic, the latter will become more apparent as the cases increase globally. SARS-CoV-2 belongs to the same group of beta-coronaviruses as SARS and MERS. It also shares 85 percent identical nucleotide sequence with the SARS virus and has similar clinical characteristics (Walls et al., 2020). Hence, understanding its clinical attributes on the nervous system is possible in light of the studies done on its earlier congeners. As the world struggles towards a biological cure or vaccination, understanding the putative mechanisms and effects of the novel coronavirus on nervous tissue and mental health will be vital for its holistic management. This narrative review (based on data from January-May 2020), attempts to highlight the potential routes of CNS spread, the neuropsychiatric sequelae and possible pathophysiological mechanisms as per the studies done in the earlier coronavirus outbreaks. For the sake of clarity, henceforth throughout the article the novel coronavirus causing COVID-19 will be referred to as SARS-CoV-2, whereas its earlier congener causing SARS will be referred to as SARS-CoV.

2. Neural spread of COVID-19: the possible routes

The SARS-CoV-2 is reported to be functionally analogous to the SARS-CoV (causative agent of SARS). The usual cellular route is viral binding to Angiotensin Converting Enzyme (ACE)-2 receptor which is widely distributed along the respiratory and gastrointestinal epithelium as well as the endothelial cell surface. The spread to central nervous system has been correlated with increased age, high viral load, poor immunity, administration of glucocorticosteroids, history of neurotrophic viral infection in the past and increased hospitalization (Singhal, 2020). Both animal and human models studying SARS-CoV have reported various possible neural pathways. The initial viral spread is hematogenous. In rodents, the virus has been detected in olfactory bulb 4 days after nasal inoculation and after 40 days in the pyriform cortex (Perlman et al., 1989). In another study by the same group, destruction of olfactory bulb prevented the neural dissemination of the coronavirus. It showed that neural proliferation can happen in the cells of cortex, hypothalamus, thalamus, amygdala, basal ganglia and interestingly also in the brain stem (Perlman et al., 1990). Dinein and kinesin are the two proteins that help in anterograde and retrograde transmission of the virus in neurons. The nucleus of the solitary fascicle in brainstem (that receives information from the chemoreceptors to alter the respiratory effort) is one of the important sites of viral load during post-mortem in animal models (Wu et al., 2020). This has been postulated as a putative theory how the virus can impair breathing-effort apart from the pulmonary involvement. Labored breathing or dyspnea is a direct clinical antecedent to Acute Respiratory Distress Syndrome (ARDS) in COVID-19, which in turn is linked to morbidity and mortality (Gattinoni et al., 2020).

3. Neuropsychiatric manifestations of COVID-19: summary of current evidence

During the first wave of infection in China, Chen et al. (2020b) described the epidemiological and clinical characteristics of 99 patients with SARS-CoV-2 pneumonia. 9 percent and 4 percent of them had confusional state and headache respectively. Few months later, Mao et al. (2020) retrospectively analyzed 214 patients with molecular diagnosis of COVID-19 from three different hospitals. 36.4 percent had neuropsychiatric symptoms, which were differentiated into central, peripheral/musculoskeletal and psychological. The central were commonest, with dizziness and headache being most prevalent. Dysgeusia, anosmia and muscle pain were most common among the peripheral symptoms. Anxiety, depression and delirium were the common psychiatric manifestations. The neurological symptoms had direct relation with the severity of the illness, serum antibody titer and blood lymphocyte counts. Also, though strokes, encephalopathies and peripheral neuropathies were rare (2 percent of the neuropsychiatric complaints), they were present in the elderly and immunocompromised group. A specific sub-group had ataxia and gait disturbances who also showed decreased CRP, impaired renal functions, poor oxygen saturation and increased need for ventilation. This was again a pointer towards brain-stem involvement. Similar blood findings have been found in children with CoV-2 infection and encephalitis (McAbee et al., 2020). It has been postulated that decreased peripheral lymphocytes can either be due to poor immunological response altogether or increased CNS tissue migration. In SARS pneumonia with related clinical findings, Granulocyte Macrophage Colony-stimulating factor (GM-CSF) had been tried as a therapeutic agent, as it helps in the generation and propagation of CNS-targeted monocytes (Verma, 2003). On similar lines, peripheral lymphocyte counts, CRP and ESR have been used as prognostic markers in COVID-19 pneumonia and GM-CSF is popularized in research as a potential therapeutic target to prevent neuropsychiatric sequelae (Zhou et al., 2020). The various neuropsychiatric manifestations that have so far been reported in COVID-19 are detailed below. As data is still emerging, various case reports and series mentioned in the literature do not necessarily imply causation but can highlight the associative neuropsychiatric impact.

3.1. Delirium and confusional states

Impaired sensorium ranging from mild drowsiness to delirium has been reported in few older adults hospitalized due to SARS-CoV-2 pneumonia, when compared to the younger participants (Liu et al., 2020). They had associated comorbidities and increased Pulmonary Severity Index (PSI). In another case series of older adults with pre-morbid cognitive decline (Beach et al., 2020), delirium was observed with COVID-19 infection which necessitated ICU admission. Unique features seen were alogia, abulia, rigidity and increased inflammatory markers. Obviously, pre-existing cognitive deficits, age, lack of stimulation, metabolic disturbances, urinary retention, constipation and prolonged hospitalization might be the associated contributing factors. Intensive care unit (ICU) delirium management and that during mechanical ventilation have been included in various treatment guidelines for COVID-19 (Xie et al., 2020). Especially in palliative care settings for COVID-19, among the most severely ill patients and elderly, the prevalence of delirium has been high. Tissue hypoxia, desaturation, neuro-inflammatory cytokines (regulating the ‘cytokine storm’ of SARS-CoV-2) and use of hydroxychloroquine has been associated with prolonged delirium in these patients (Wu and McGoogan, 2020). Effective management of sleep disturbance and early correction of sensorium are reported to be vital in post intensive care syndrome (PICS) and decreasing morbidity. Melatonin is being studied to have a promising role for the same in COVID-19 patients (Zhang et al., 2020a).
3.2. Dysfunction of olfaction and taste sensation

During the SARS outbreak, studies have shown its affinity for the nasal ciliary epithelium. This property has been theorized to be common in the CoV group (Chilvers et al., 2001). In fact, the ACE-2 receptor that is the target for SARS-CoV-2 is expressed in the olfactory lining as well. This might be a probable mechanism for anosmia or hyposmia early in the COVID-19 infection, though the exact pathways are still being studied. The proportion of cases having olfactory and gustatory disturbances have ranged from 12 to 32 percent in a multi-site European study of COVID-19 cases (Lechien et al., 2020). Olfactory dysfunction has even been considered as a biomarker for COVID-19 infection (Moein et al., 2020). They proposed that the predilection for the gustatory chemoreceptors and the higher order centers involved in taste and smell perception are more for the SARS-CoV-2 than its earlier congeners. Hyposmia has also been proposed as an early marker of neurological involvement in COVID-19 based on a European case-series, though structured research is yet to be done (Vaira et al., 2020). Post-viral olfactory syndrome, a known complication of Influenza and Herpes virus infections, can also be associated with COVID-19, as the cribiform plate penetration and pyriform cortex involvement is common for all.

3.3. Acute psychosis and manic disorders

So far, there have been only two case reports mentioning acute psychotic disturbances in cases of COVID-19, one of whom had schizophrenia (Fischer et al., 2020; Zulkifli et al., 2020). However, many known patients of schizophrenia have had exacerbations after getting affected with SARS-CoV-2 even while on medications (Yao et al., 2020). Whether there is a neuro-biological basis to it is unclear. The study by Mao et al. (2020) mentioned people to have behavioural disturbances. SARS infection has been associated with acute psychiatric manifestations with increased antibody titer, which points out a probable relationship between coronavirus infections and psychosis (Cheng et al., 2004). The CoV also proliferates in the limbic structures, as shown in animal models that further supports its association with behavior (Subbarao and Roberts, 2006). Also, there has been debate whether vertical transmission is likely in COVID-19 positive mothers that can increase the neuro-developmental risk of psychosis in their off spring, similar to influenza (Qiao, 2020). As multiple issues like drug compliance, lack of review, poor awareness and stress diathesis are involved during any biological disaster, it is difficult to conceptualize a direct link between increase of pre-existing psychiatric illnesses and the neurotropic effects of the virus.

3.4. Encephalitis and encephalopathies

The classic Von Economo’s encephalitis (1917) during the Spanish flu pandemic traditionally marks the association of viral infections and the brain. It was characterized by increased somnolence, behavioral disturbances, catatonic states and movement disorders. Similar encephalitis sequelae with altered consciousness have been reported during the H1N1 influenza and MERS infection (Alakare et al., 2010). Though initially reported as a rare association in the current pandemic, multiple case reports of encephalitis have been reported since the first wave of infection. Moriguchi et al. (2020) reported the first case of meningoencephalitis in a COVID-19 patient with recent onset convulsions, who showed hyperintensity of bilateral mesial temporal lobes on brain imaging. Of special interest was a case of acute necrotizing haemorrhagic encephalopathy in a woman affected with COVID-19 where magnetic resonance tomography (MRT) of the brain showed rim-enhancing lesions in bilateral thalami, medial temporal lobes and sub-insular regions (Poyiadji et al., 2020). The ‘cytokine storm’ responsible for ARDS and multi-organ dysfunction syndrome (MODS) in COVID-19 is marked by the surge of inflammatory cytokines in the circulation namely Interleukins (IL)-6, 8, 10, 18, Tumour Necrosis Factor (TNF)-alpha, Interferon-gamma and GM-CSF (Mehta et al., 2020). Most of these factors were increased in 20 percent of COVID-19 positive cases in the study reported by Chen et al. (2020a,b,c), who were diagnosed to have persistent encephalopathy. The association of exaggerated cell-mediated immunity with encephalitis has been studied in SARS as well (Huang et al., 2005). Especially in the COVID-19 patients receiving intensive care and ventilation, increased somnolence, agitation and confusion have been seen in those who had increased blood cytokines (Yang et al., 2020). Further, factors like pre-existing cognitive deficits, age and chronic psychiatric illness can increase the post-ICU recovery time and lead to long-lasting neuropsychological sequelae in such patients. Overall, encephalopathy has been considered to be the most serious acute neurological effect of COVID-19, as steroids (an important component of treatment) are restricted due to the pulmonary decompensation.

3.5. Acute cerebrovascular events

In the retrospective study by Mao et al. (2020) among SARS-CoV-2 pneumonia cases, six patients reported acute cerebrovascular accident (CVA), in which most were ischemic strokes that developed within a week of pulmonary presentation. Another study of neurological symptoms in COVID-19 mentioned acute CVA to be more associated with the elderly, lower platelet count and increased D-dimer levels (Liu et al., 2020b). A case-series from United States (US) reported four elderly patients of COVID-19 who presented to the emergency with stroke, three of them had no prior CVA or associated risk factors (Ayula et al., 2020). A probable mechanism might be viral effects on the ACE-2 receptors on the endothelial cells and platelets that can lead to hypertension and hyper-coagulable states respectively. But the cause or effect dilemma is debatable. On the other side, recurrent CVA has also been mentioned as a risk for severe COVID-19 infections. A pooled analysis of the published literature showed a 2.5-fold increase in the risk of severe C0V-2 infection in stroke patients (Aggarwal et al., 2020). However, there was no significant association between stroke and mortality due to COVID-19. A case series by Oxley et al. (2020) reported five young patients presenting with stroke and comorbid COVID-19. A comparative theoretical analysis of non-human primate pathogenesis model in SARS, MERS and COVID-19 has implicated the SARS-CoV-2 spike protein to have a neuro-inflammatory role contributing to endothelial dysfunction and blood stasis (Rockx et al., 2020). Though evidence is equivocal, this study warned about the potential role of ACE-inhibitors and ibuprofen in facilitating coronavirus infections. A recent study from Netherlands demonstrated that 31 percent of ICU patients developed thrombotic complications (Klok et al., 2020). Another study concluded that thromboplastin time-based clot waveform analysis (CWA) can determine hypercoagulability and risk of strokes associated with high viral loads in COVID-19 (Tan et al., 2020). Multiple reports of pulmonary embolism are also available (Chen et al., 2020a; Danzi et al., 2020). Keeping in mind this probable bi-directional relationship, separate guidelines have emerged for stroke management during the times of COVID-19. Khosravani et al. (2020) has also proposed a Protected Code Stroke (PCS) framework during the ongoing pandemic which modifies the screening guidelines and includes rational use of personal protective equipment (PPE) and crisis management.

4. Possible neuropsychiatric sequelae of COVID-19: insights from earlier CoV studies

The COVID-19 pandemic is still in its early stages. The human-human transmission is higher than its earlier congeners (Singhal, 2020) and the projected spread is ominous. As efforts for containment are on the rise, the upcoming months and years will add more to the understanding of long-term neuropsychiatric sequelae in COVID-19. Even if that affects a less proportion of cases, it is going to be associated with an immense public health burden. The SARS and MERS outbreaks also had
The initial flattening of curve might be assuring for the spread of the pandemic, as health-care priorities change with the timing of the outbreak. As such, the SARS-CoV-2 infection and post-mortem studies have shown increased viral ribonucleic acid (RNA) load. A study by Wu et al. (2020) attributed the demyelinating effect of coronavirus to tissue hypoxia, direct neuronal injury, neuro-inflammation and major histocompatibility complex (MHC) mediated cell-mediated-immune (CMI) response to the virus. Murine models have shown the neuro-muscular concentration of the viruses to be strain dependent (Henderson et al., 2020). Peripheral neuropathies in COVID-19 have been reported in few cases across the globe (Abdelnour et al., 2020). A comprehensive review of neurological symptoms in coronavirus diseases mentions COVID-19 as a potential risk factor for long-term demyelinating and neuromuscular conditions (Troyer et al., 2020).

4.1. Neuromuscular disorders

Viral infections involving the brain are known to cause myopathy, neuropathy, GBS and brainstem encephalitis (Arciniegas and Anderson, 2004). These often take a month to manifest after the respiratory complaints. Multiple sclerosis patients had shown worsening during the SARS-CoV-2 infection and post-mortem studies have shown increased viral ribonucleic acid (RNA) load. A study by Wu et al. (2020) attributed the demyelinating effect of coronavirus to tissue hypoxia, direct neuronal injury, neuro-inflammation and major histocompatibility complex (MHC) mediated cell-mediated-immune (CMI) response to the virus. Murine models have shown the neuro-muscular concentration of the viruses to be strain dependent (Henderson et al., 2020). Peripheral neuropathies in COVID-19 have been reported in few cases across the globe (Abdelnour et al., 2020). A comprehensive review of neurological symptoms in coronavirus diseases mentions COVID-19 as a potential risk factor for long-term demyelinating and neuromuscular conditions (Troyer et al., 2020).

4.2. Chronic psychiatric conditions

There have been worsening of pre-existing psychiatric conditions namely mood and bipolar disorders, especially in the vulnerable populations. Increased incidence of depression, anxiety, adjustment disorders, acute stress reaction, somatization and obsessive-compulsive disorders have also been reported (Rajkumar, 2020). Whether they are due to the adverse psychosocial situations and uncertainty of the pandemic crisis or whether the virus has a direct effect on the brain contributing to this, has not been well studied. Animal models have shown increased behavioral problems and poor performance in maze-finding, social play, mating and learned helplessness tasks after nasal inoculation of coronavirus (Fung and Liu, 2014). The translation to humans is still far-fetched. The mood disorders consequent to the SARS epidemic were related to host immune reaction (Hui et al., 2009). Recent studies among COVID-19 patients have found greater occurrence of depressive and anxiety disorders in people who are in quarantine, front-line workers or among family members of affected patients (Qu et al., 2020). However, the biological markers for same have not yet been studied. Okusaga et al. (2011) while studying people with SARS-CoV infection, found exacerbations of mood disorders and psychosis in the long run but no association with the typology, mood polarity or suicidality. However, pandemic responses have classically been associated with marked increase in psychiatric morbidity. There has been specific rise in pain, depressive, obsessive compulsive disorders (OCD) and post-traumatic stress disorders (PTSD). The PTSD following such biological disasters might often be complex and chronic, unlike the commonly described ones. As time progresses, with the global burden of SARS-CoV-2 infection, more data on the psychiatric consequences of this pandemic are expected to come.

4.3. Neurodegenerative disorders

There is a theoretical risk for any coronavirus infected patient to develop Parkinson’s like features, as the virus has been shown to proliferate in the basal ganglia in murine models (Fishman et al., 1985). Borrowing from the motor involvement in ‘encephalitis lethargica’, movement disorders can be potential risk for any neurotrophic viral infection. Anti-CoV antibodies found in the cerebrospinal fluids of patients with motor disorders might have been incidental (Fazzini et al., 2020).

Table 1

| Mechanism of pathogenesis | Details | Neuropsychiatric effects |
|---------------------------|---------|-------------------------|
| Direct injury (Blood circulation) | Exaggerated immune response | Encephalopathy |
| Direct injury (Neuronal route) | Cytokines increasing blood-brain-barrier (BBB) permeability | Delirium and acute confusional state |
| Hypoxic injury | Predilection for olfactory epithelium, bulb and vagal centers | Anosmia |
| Dysregulated immunomodulation | Anterograde and retrograde neural proliferation via dynein and kinesin | Dysequilibrium |
| Immune cell transmigration to CNS | Structural preference for the forebrain, basal ganglia and hypothalamus | Psychiatric disorders |
| ACE-2 and CoV spike protein interaction | Impaired pulmonary exchange and pulmonary oedema can cause cerebral hypoxia | Encephalopathy |
| Autoimmunity | Cerebral oedema, vasodilation, ischaemia and vascular congestion | Somnolence |
| Miscellaneous | Increased intracranial pressure | Coma |
| | | Headache |
| | | Confusion |
| | | Encephalitis |
| | | MODS |
| | | Acute psychosis |
| | | Seizures |
| | | Both acute and chronic neuropsychiatric effects |
| | | Cerebro-vascular accidents |
| | | Pulmonary and cerebral venous thrombembolism |
| | | Risk of chronic neurodegeneration |
| | | Demyelination |
| | | GBS |
| | | Neupathy |
| | | Persistent or relapsing-remitting neurological sequelae |
| | | Reactivation of seizures |
| | | Chronic psychiatric conditions |
1992), as no clear literature is present about association of clinical Parkinson’s disease with CoV infections. Also, considering coronavirus can stay latent in neural tissue for a long time (Johnson, 1984), there might be a plausible risk for chronic degenerative conditions like dementia in the long run.

4.4. Epilepsy

Encephalopathy or cerebral edema consequent to CoV pathogenesis can lead to new-onset seizures or reactivation of latent epilepsy (Wu et al., 2020). The associated psychological stress can also be a triggering factor. A couple of case reports mention patients with COVID-19 presenting with generalized tonic-clonic seizures (Karimi et al., 2020; Sohal and Mossammat, 2020). One however had the primary diagnosis of encephalitis. Drug compliance risks during pandemics can increase the risk of status epilepticus, as reported earlier during the SARS outbreak (Lai et al., 2005). Certain anti-virals like remdesivir and lopinavir that have been used in COVID-19 patients can have cytochrome-based interactions with common anti-epileptics. The direct epileptogenic potential of CoV is however not established.

5. Neuropsychiatric effects of COVID-19: possible pathogenic mechanisms

Even though research in this field has just begun, based on the pathogenic models of the earlier CoV infections, here are some possible mechanisms in which SARS-CoV-2 might cause the above-mentioned manifestations. These are summarized with the evidence as under (Table 1).

6. Conclusion

The numbers of cases infected with SARS-CoV-2 are rising each day. The public health systems of countries around the world were unprepared for a pandemic of such unprecedented scale. The pulmonary symptoms being on the forefront are the prime focus of treatment at present. It has however been shown from past outbreaks of CoV, that the neuropsychiatric symptoms arising out of the viral infection can act significantly to the health burden and quality of life (Chua et al., 2004; Honigshbaum, 2013). The emerging data related to the neuropsychiatric manifestations of COVID-19 are reviewed in this paper with other likely sequelae which has yet not been reported. As mentioned before, much of the current data is derived from case reports and series, which need to be interpreted with caution. They can imply association at maximum, not causation, which need more systematic researches. The proposed mechanisms are speculative, however as SARS-CoV-2 shares a lot of structural and functional similarities with the earlier congeners of the CoV family, studies done in SARS and MERS can help researchers glance into the current pathogenesis and thereby prepare management plans. The use of steroids in COVID-19 is increasing and they need to be monitored for the risk of worsening neuropsychiatric symptoms (Shang et al., 2020). Other immune-modulatory measures like intravenous immunoglobulin (IVIG), GM-CSF and interleukin-inhibitors are currently being tried in COVID-19 (Zhang et al., 2020b). Considering the putative neuro-inflammation involved, these agents might also hold a structural and functional similarities with the earlier congeners of the present. It has however been shown from past outbreaks of CoV, that the possible solutions.

Author contribution
Both the authors contributed equally to the conceptualization of the study, literature review, planning, drafting and editing the manuscript. The final version of the manuscript has been read and approved by both the authors.

Ethical statement
No participants were recruited for the study.

Declaration of Competing Interest
The authors report no declarations of interest.

Acknowledgment
None.

References
Abdennour, L., Abdalla, M.E., Babiker, S., 2020. COVID-19 infection presenting as motor peripheral neuropathy. J. Formos. Med. Assoc. 119 (6), 1119–1120.
Abdennour, L., Zeghal, C., Dene, M., Puyhaubert, L., 2012. Interaction brain-lungs. In: Annales francaises d’anesthesie et de reanimation, Vol. 31, pp. e101–107. June, No. 6.
Aggarwal, G., Lippi, G., Michael Henry, B., 2020. Cerebrovascular disease is associated with an increased disease severity in patients with Coronavirus Disease 2019 (COVID-19): a pooled analysis of published literature. Int. J. Stroke 15 (4), 385–389. p.174793020291664.
Alakare, J., Jurkko, R., Kaukonen, K.M., Saatamoinen, K., Räcklund, T., Kaartinen, J., Kolho, K., Harjola, V.P., 2020. Viral encephalitis associated with pandemic 2009 (H1N1) influenza A. Case Rep. 2010 p.bcr2010127722.
Arciniegas, D.B., Anderson, C.A., 2004. Viral encephalitis: neuropsychiatric and neurobehavioral aspects. Curr. Psychiatry Rep. 6 (5), 372–379.
Avula, A., Nalleballe, K., Narula, N., Sapushnikov, S., Dandu, V., Toon, S., Glaser, A., Elsayegh, D., 2020. COVID-19 presenting as stroke. Brain Behav. Immun. 87 (July 2020), 115–119.
Banerjee, D., 2020. How COVID-19 is overwhelming our mental health. Nat. India 26 (March), 2020. Retrieved.
Beach, S.R., Praschan, N.C., Hogan, C., Dotson, S., Merideth, F., Konto, N., Frickione, G.L., Smith, F.A., 2020. Delirium in COVID-19: a case series and exploration of potential mechanisms for central nervous system involvement. Gen. Hosp. Psychiatry 65 (July-August 2020), 47–53.
Bender, S.J., Phillips, J.M., Scott, E.P., Weiss, S.R., 2010. Murine coronavirus receptors are differentially expressed in the central nervous system and play virus strain-dependent roles in neural spread. J. Virol. 84 (21), 11030–11044.
Bohnwald, K., Galvez, N., Ass, M., Klearvig, A.M., 2018. Neurologic alterations due to respiratory virus infections. Front. Cell. Neurosci. 12, 386.
Chan, J.F.W., Zhang, A.J., Yuan, S., Poon, V.K.M., Chan, A.C.Y., Chan, W.M., Fan, Z., Tao, H.W., Wei, L., Liang, R., 2020. Simulation of the clinical and pathological manifestations of Coronavirus Disease 2019 (COVID-19) in golden Syrian hamster model: implications for disease pathogenesis and transmissibility. Clin. Infect. Dis. ciaa325 (March 2020).
Chen, J., Wang, X., Zhang, S., Liu, B., Xu, W., Wang, Y., Wang, X., Yang, M., Sun, J., Xie, Y., 2020a. Findings of Acute Pulmonary Embolism in COVID-19 Patients. Available at SSRN 3548771.
Chen, N., Zhou, M., Dong, X., Qu, J., Gong, F., Han, Y., Qiu, Y., Wang, J., Liu, Y., Wei, Y., Yu, T., 2020b. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet 395 (10223), 507–513.
Chen, Q., Liang, M., Li, Y., Guo, J., Fei, D., Wang, L., He, L., Sheng, C., Cai, Y., Li, X., Wang, J., 2020c. Mental health care for medical staff in China during the COVID-19 outbreak. Lancet Psychiatry 7 (4), e15–e16.
Cheng, S.K.W., Tsang, J.S.K., Ku, K.H., Poon, V.K.M., Chau, C.S.L., Chan, A.C.Y., 2004. Neurological complications in patients with severe acute respiratory syndrome (SARS) during the acute treatment phase: a series of 10 cases. Br. J. Psychiatry 184 (4), 359–360.
Chilvers, M.A., McKean, M., Rutman, A., Myint, B.S., Silverman, M., 2005. The effects of coronavirus on human nasal ciliated respiratory epithelium. Eur. Respir. J. 18 (6), 965–970.
Chua, S.E., Cheung, Y., McAlonan, G.M., Cheung, C., Wong, J.W., Cheung, E.P., Chan, M.T., Wong, T.K., Choy, K.M., Chu, C.M., Lee, P.W., 2004. Stress and psychological impact on SARS patients during the outbreak. Can. J. Psychiatry 49 (6), 385–390.
Duniz, G.B., Loffi, M., Galeazzi, G., Gherbesi, E., 2020. Acute pulmonary embolism and COVID-19 pneumonia: a random association? Eur. Heart J. 41 (10), 1858–1858.
Desforges, M., Le Coupanec, A., Debeau, P., Bourgoun, A., Lajoie, L., Dubé, M., Talbot, P.J., 2020. Human coronaviruses and other respiratory viruses: underestimated opportunistic pathogens of the central nervous system? Viruses 12 (1), 14.
Yang, J., Zheng, Y., Gou, X., Pu, K., Chen, Z., Guo, Q., Ji, R., Wang, H., Wang, Y., Zhou, Y., 2020. Prevalence of comorbidities in the novel Wuhan coronavirus (COVID-19) infection: a systematic review and meta-analysis. Int. J. Infect. Dis. 94 (May), 91–95.

Yao, H., Chen, J.H., Xu, Y.F., 2020. Patients with mental health disorders in the COVID-19 epidemic. Lancet Psychiatry 7 (4), e21.

Zhang, R., Wang, X., Ni, L., Di, X., Ma, B., Niu, S., Liu, C., Reiter, R.J., 2020a. COVID-19: melatonin as a potential adjuvant treatment. Life Sci. 117583.

Zhang, W., Zhao, Y., Zhang, F., Wang, Q., Li, T., Liu, Z., Wang, J., Qin, Y., Zhang, X., Yan, X., Zeng, X., 2020b. The use of anti-inflammatory drugs in the treatment of people with severe coronavirus disease 2019 (COVID-19): the experience of clinical immunologists from China. Clin. Immunol. 108393.

Zhou, M., Zhang, X., Qu, J., 2020. Coronavirus disease 2019 (COVID-19): a clinical update. Front. Med. 1–10.

Zulkifli, N.A., Sivapatham, S., Guan, N.C., 2020. Brief psychotic disorder in relation to coronavirus, COVID-19 outbreaks: a case report. Malaysian J. Psychiatry 29 (1).