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Review article

Update on neurological manifestations of COVID-19

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ARTICLE INFO

Keywords:
Novel coronavirus
Nervous system
Neurological symptoms
Neuroinvasion

ABSTRACT

Novel coronavirus (severe acute respiratory syndrome coronavirus-2: SARS-CoV-2) has a high homology with other cousin of coronaviruses such as SARS and Middle East respiratory syndrome-related coronavirus (MERS). After outbreak of the SARS-CoV-2 in China, it has spread so fast around the world. The main complication of coronavirus disease 2019 (COVID-19) is respiratory failure, but several patients have also been admitted to the hospital with neurological symptoms. Direct invasion, hematogenic rout, retrograde and anterograde transport along peripheral nerves are considered as main neuroinvasion mechanisms of SARS-CoV-2. In the present study, we describe the possible routes for entering of SARS-CoV-2 into the nervous system. Then, the neurological manifestations of the SARS-CoV-2 infection in the central nervous system (CNS) and peripheral nervous system (PNS) are reviewed. Furthermore, the neuropathology of the virus and its impacts on other neurological disorders are discussed.

1. Introduction

Coronavirus disease 2019 (COVID-19) is a pandemic crisis with the ability to kills millions of people. Novel coronavirus (severe acute respiratory syndrome coronavirus-2: SARS-CoV-2) was first detected in China on 12 December 2019 and has rapidly spread among rest of the world [1]. The SARS-CoV-2 belongs to Beta-coronavirus family, ranging from 26 to 32 kilobases in length. The RNA virus is enveloped with a positive sense single-stranded RNA genome [2]. There is a closest linkage between two SARS-like coronaviruses from bat. Four structural proteins are considered for the virus as (E) the envelope protein, (M) the membrane protein, (S) the spike protein, and (N) the nucleocapsid protein [3]. Angiotensin converting enzyme 2 (ACE2) is a receptor on the human cells surface and it has been shown that SARS-CoV virus, the other cousin of COVID-19, binds to this receptor with its spike protein for entering to the cells. Based on the recent research, ACE2 is also required for SARS-CoV-2 entry into the cells [4]. The ACE2 shows widespread distribution in different organs including brain and neural cells [5]. Clinical symptoms of COVID-19 are range from mild to severe. Fever, cough, and shortness of breath are the most common symptoms of the disease [6].

According to the clinical observation in 2019, the SARS-CoV-2 invades the central nervous system (CNS) and in this way, presumably affects pulmonary function. Respiratory center in the brainstem is considered as a main target of SARS-CoV-2 which leads to respiratory center dysfunction and consequent acute respiratory distress in COVID-19 patients [7]. Although most studies have focused on the respiratory manifestation of COVID-19, but regarding the recent SARS-CoV-2 outbreak, the neurological manifestations of this virus are becoming more and more evident.

The SARS-CoV-2 shows high homology in both genomic sequence and clinical manifestations with SARS-CoV and MERS-CoV. Previous clinical and experimental evidence suggested that brain is a major target of the coronaviruses [3]. These viruses have also been detected in the cerebrospinal fluid (CSF) of SARS and MERS infected patients in the early 2000s [8]. Moreover, SARS-CoV virus antigen was detected abundantly in the olfactory bulb, piriform and infra-limbic cortices, basal ganglia (ventral pallidum and lateral preoptic regions), and midbrain (dorsal raphe) in the infected patients [9]. Due to the mentioned similarities between SARS-CoV-2 and other beta coronaviruses, it is not unexpected that COVID-19 patients show the neurological symptoms and complications. Many patients with novel coronavirus have reported different range of neurological symptoms from mild and non-specific symptoms such as headache, nausea, vomiting, languidness, myalgia, and unstable walking to more complex symptoms like cerebral hemorrhage, meningitis, encephalitis, and other neurological complications [10,11].

It has been indicated that SARS-CoV-2 may enter to the CNS through...
hematicogenous rout, retrograde or anterograde neuronal transport [12,13]. Understanding the virus neuroinvasion pathway help researchers to better identify pathological related consequences of infection and in this way, the diagnostic criteria as well as management and treatment of the disease can be improved.

In this review article, we summarize the mechanism of SARS-CoV-2 entry, neurological symptoms of the COVID-19 infection in central nervous system (CNS) and peripheral nervous system (PNS), immune neuropathology of the virus, and the impacts of the virus on other neurological disorders.

2. The SARS-CoV-2 entering mechanisms to the nervous tissue

Although there are several suggested routs for entering of the SARS-CoV-2 to the nervous system, the exact mechanism of its neuroinvasion is not clear. The virus may directly invade the nervous tissue because of its detection in the CSF or brain tissue. In order to invade different organs, the SARS-CoV-2 may spread through the bloodstream. Viremia results in virus transcytosis across the endothelial cells of blood brain barrier (BBB) or the virus infects epithelial cells of the blood-cerebrospinal fluid barrier (BCSFB) in the choroid plexus (CP) of the brain ventricles. Moreover, leukocytes may be infected and transport the virus as a vector. In order to access the CNS, the virus uses the axonal transport machinery (retrograde transport). In addition to hematic rout, lymphatic rout is also considered to be a possible pathway for the virus to enter the CNS. Direct viral invasion is another hypothesis for the entering of virus to the CNS. The SARS-CoV-2 may invade the nervous tissue through the ACE2 or TMPRSS2 receptors. These receptors have shown wide distribution in the body. Interestingly, the ACE2 receptor is also expressed on the membrane of spinal cord and the virus may invade the spinal cord through its binding to the ACE2 receptors on the surface of neurons [14,15]. The SARS-CoV-2 may penetrate cribiform plate close to the olfactory bulb (OB) and the olfactory epithelium (OE). In this way, virus enters to the CNS. Anosmia or hyposmia as new presentations of COVID-19 patients confirm this route of infection. Moreover, COVID-19 patients show severe hypoxia and increased leukocyte migration. In this process, the virus doesn’t have direct invasion or para-infectious demyelination [30].

Hypoxia is another process which results in nervous tissue damage. Virus proliferation and subsequent alveolar dysfunction lead to hypoxia in the CNS. Additionally, increased anaerobic metabolism, cerebral vasodilatation, cerebral blood supply obstruction, and headache due to ischemia and congestion are occurred following virus infection. If the hypoxia continues, the brain function worsens and may even lead to coma or death [31]. Severe hypoxia also may result in acute cerebrovascular disorder such as acute ischemic stroke [32]. It has also been demonstrated that COVID-19 patients often show severe hypoxia and viremia which increase the risk of toxic encephalopathy [32]. Since, COVID-19 cases often suffer from severe hypoxia, this process may play a critical role in the nervous system damage following virus infection [33].

It has been shown that patients with COVID-19 lose senses of smell and taste. The smell loss may be due to direct damage to the olfactory bulb and the inflammatory response in the nasal cavity, which blocks the binding of odorsants to the olfactory receptors. It takes a long time for damaged neurons to form successful synapses with the olfactory bulb [34]. Regarding to taste sense dysfunction, cytokines molecules in COVID-19 patients may target taste buds and cause ageusia [35]. Another hypothesis for altered taste sense is related to ability of SARS-CoV-2 for occupying sialic acid binding site on the taste buds which results in accelerating the degradation of the gustatory particles [35].

Fig. 1 shows the immune pathogenesis of SARS-CoV-2.

4. CNS manifestation of the COVID-19

It has been shown that SARS-CoV-2 infects the brain and spinal cord of the patients. The first case of spinal cord involvement was observed in a 66-year-old man with a post-infectious acute myelitis presentation. Acute myelitis was diagnosed due to the acute flaccid myelitis of lower limbs, urinary and bowel incontinence, and sensory level at T10. Moreover, any obvious abnormality in cranial nerve examination was not reported [15]. In a retrospective, observational case series study, Mao et al. evaluated 214 confirmed SARS-CoV-2 patients for their neurological manifestation. The patients have manifested for both CNS and PNS symptoms as well as skeletal muscle injury and among those, CNS symptoms were the predominant form of neurologic manifestation in patients with COVID-19. It has also been noted that neurological dysfunction was greater in those with severe infection. Higher level of D-dimer was observed in cases with severe infection compared to patients with non-severe infection which might be considered for the higher incidence of cerebrovascular disease in patients with severe infection. Furthermore, patients with CNS symptoms had lower levels of lymphocyte count that shows immunosuppression in these patients [10]. In a single-center retrospective study, a number of 221 COVID-19
patients were analyzed for presenting new onset acute cerebrovascular disease (CVD). Among those, 13 patients showed CVD. Patients with CVD were older and had many risk factors such as hypertension and diabetes, and higher level of C-reactive protein compared to patients without CVD [36]. Moriguchi et al. reported the first case of meningitis/encephalitis in COVID-19 patients. Magnetic resonance imaging (MRI) revealed an abnormal presentation of medial temporal lobe including hippocampus which indicates encephalitis, hippocampal sclerosis or post convulsive encephalitis. The patient also showed pansinusitis and paranasal sinusitis. In order to better and earlier diagnose of SARS-CoV-2 infection, it is important to pay more attention to the nasal and paranasal conditions [13]. Sohal et al. reported seizures in a 72-year-old man patient with COVID-19 infection. However, chronic microvascular ischemic alteration was detected in computed tomography (CT) of the head, but there was no evidence of infarct or hemorrhage [37]. Another report of seizure in COVID-19 patients was studied in a 30-year-old female. This patient was presented with generalized tonic-clonic seizure. Brain MRI was normal and her seizures were recurring (five times) approximately every 8 h [38]. Filatov et al., reported encephalopathy in a 74-year-old male who was positive for COVID-19. No acute abnormalities were observed in the CT of the head and EEG findings was consistent with an encephalopathy and focal left temporal lobe dysfunction. However, the CSF analysis was normal [39]. A 54-year-old patient with SARS-CoV-2 infection was reported with specific neurological manifestation. The brain CT showed bilateral basal ganglia involvement and a subacute hemorrhagic insult [40]. Pilotto et al. reported a 60-year-old man presented with severe alteration of consciousness. The patient diagnosed with encephalopathy and his laboratory testing showed an increased level of D-dimer. The CSF analysis revealed a mild lymphocytic pleocytosis and the CSF proteins were increased [27]. Encephalitis associated with SARS-CoV-2 was also reported in a male COVID-19 patient. He was positive for meningeal irritation signs including nuchal rigidity, Kernig sign, and Brudzinski sign and extensor plantar response [28]. Acute necrotizing hemorrhagic encephalopathy is a rare encephalopathy associated with viral infection. This rare manifestation was reported in a female airline worker in her late fifties with COVID-19 infection. She was admitted to the hospital with altered mental status. Her CT of the head showed symmetric hypo-attenuation of the bilateral medial thalami and the MRI images indicated T2 FLAIR hyper-intensity of the bilateral medial temporal lobes and thalami. This is the first reported case of COVID-19 patient with acute necrotizing hemorrhagic encephalopathy [30]. Lau et al. reported a possible involvement of the CNS by the SARS-CoV-2 in a 32-year-old pregnant woman with myalgia manifestation. The patient showed generalized convulsion which is probably due to the infection of the CNS [41].

5. PNS manifestation of the COVID-19

It has been shown that the SARS-CoV-2 can involve the peripheral nervous system. Anosmia and taste-related changes are as indications of SARS-CoV-2 infection. These manifestations support the idea of olfactory invasion route of SARS-CoV-2 virus. The first case of COVID-19 patient with an olfactory dysfunction was about a 40-year-old woman with sudden and complete loss of the olfactory function. She had experienced dry cough related to cephalagia and myalgia. Her MRI showed bilateral inflammatory obstruction of the olfactory clefts [42]. The prevalence of smell and taste alteration in hospitalized patients with COVID-19 were calculated about 34% in a study [43]. However, they didn't report any data on these symptoms timing of onset compared to other symptoms. In line with this study and to overcome the data insufficiency, a cross sectional study on 202 patients with SARS-CoV-2 was performed and prevalence, intensity, and timing of an altered sense of smell or taste in COVID-19 patients were analyzed. The results indicated that 130 patients (64.4%) show altered sense of smell or taste. Of these 130 patients, 45 patients (34.6%) also reported blocked nose. Regarding the timing of alteration in sense of smell or taste onset compared to other symptoms, they reported that 24 patients (11.8%) before other symptoms, 46 patients (22.8%) at the same time and 54 patients (26.7%) after other symptoms showed taste and smell

Fig. 1. The immune pathogenesis of COVID-19 in the CNS.

Hypoxia is considered as a key player in COVID-19 associated CNS pathology. Alveolar dysfunction results in brain hypoxia that is followed by cerebral vasodilation, increased anaerobic metabolism, and ischemia. On the other hand, over-activation of the immune system and increased release of inflammatory cytokines and chemokines such as interleukins 2, 6, 7, and 10, tumor necrotizing α, and granulocyte colony-stimulating factor change the blood brain barrier permeability and these factors allow the virus to enter into the central nervous system. Moreover, some of these cytokines activate glutamate receptors and cause neuronal hyper-excitability, leading to acute seizures.
| Case demographic | Diagnosis | General sign & symptoms | Medical history | CT scan of the head | MRI | EEG | Laboratory testing | CNS & PNS involvement | CSF analysis | Treatment | Results | Ref. |
|------------------|-----------|--------------------------|----------------|-------------------|-----|-----|-------------------|-----------------------|--------------|-----------|---------|------|
| A 54-year-old woman | Encephalopathy with brain basal ganglia involvement | Cough for the past five days, low-grade fever | Diabetes, hypertension, a history of lumbar spinal laminctomy and fusion surgery | Acute to subacute changes evident of bilateral basal ganglia hyper density | Not reported (N.R) | White blood cell count was within the reference range, serum and urine ketones were negative, All electrolytes were in the reference range, blood glucose level was 250 mg/dL | | Sudden and complete loss of the olfactory function without nasal obstruction | impossible due to previous lumbar surgeries and scarring | Hydroxychloroquine, levofloxacin, naproxen, oral lopinavir/ritonavir | The patient's vital signs and general condition stabilized | [40] |
| A 74-year-old male | Encephalopathy | Fever and cough | Atrial fibrillation, cardioembolic stroke, Parkinson’s disease, chronic obstructive pulmonary disease (COPD), and recent cellulitis | No acute changes, There is an area of hypo density in the right temporal region | N.R | Diffuse slowing and focal slowing, sharply contoured waves in the left temporal region | N.R | Headache, altered mental status | Showed no evidence of CNS infection | Vancomycin, meropenem, acyclclovir, hydroxychloroquine lopinavir/ritonavir | N.R | [39] |
| A 66-year-old man | Post-infectious acute myelitis | Fever and fatigue, no obvious abnormality in cranial nerve examination | Bilateral basal ganglia and paraentrical lacunar infarction, brain atrophy | Not performed (NP) | Positive nasopharyngeal swab for COVID-19, elevated levels of ALT and AST | Acute flaccid paralysis of bilateral lower limbs, urinary, bowel incontinence | N.P | | Ganciclovir, lopinavir/ritonavir, meropenem, dexamethasone, human immunoglobulin and mecobalamin | Bilateral lower extremities were ameliorated | [15] |
| A 24-year-old man | Meningitis/encephalitis associated with SARS-CoV-2 | Generalized fatigue and fever, sore throat, paranasal sinusitis | No episodes of mesial temporal epilepsy | Hyper intensity along the wall of inferior horn of right lateral ventricle, hyper intense signal changes in the right mesial temporal lobe and hippocampus with slight hippocampal atrophy | N.P | Increased white cell count, Neutrophil dominant, decreased lymphocytes, increased C-reactive protein | Unconsciousness, transient generalized seizures, neck stiffness | Specific SARS-CoV-2 RNA was detected in CSF, The CSF cell count was 12/μL – 10 mononuclear and 2 polymorphonuclear cells without red blood cells | Intravenous (IV) ceftriaxone, vancomycin, aciclovir and steroids, intravenous levetiracetam, faviaprazir | N.R | [13] |
| A 72-year-old man | Seizures | Weakness, lightheadedness after experiencing a hypoglycemic episode, fever | Hypertension, coronary artery disease with stent, diabetes type 2, and stage kidney disease on hemodialysis | Chronic microvascular ischemic changes but did not show any acute changes infarct or hemorrhage | MBI brain was not completed due the patient being too unstable for transport | Six left temporal seizures and left temporal sharp waves which were epileptogenic | Elevated CRP, lymphopenia, leukocytosis, elevated Troponin | Multiple episodes of tonic colonic movements of his upper and lower extremities | Patient died before lumbar puncture could be arranged | Hydroxychloroquine and azithromycin, vancomycin and piperacillin tazobactam, valproate | Died | [37] |

(continued on next page)
| Case demographic | Diagnosis | General signs & symptoms | Medical history | CT scan of the head | MRI | EEG | Laboratory testing | CNS & PNS involvement | CSF analysis | Treatment | Results | Ref. |
|------------------|-----------|-------------------------|-----------------|-------------------|-----|-----|-------------------|----------------------|--------------|-----------|--------|------|
| 30-year-old female | Frequent convulsions | Dry cough, fever and fatigue | No past medical history | NP | Brain MRI was normal | NP | Mildly elevated erythrocyte sedimentation rate (ESR = 35 mm/h), normal C-reactive protein (CRP), white blood cell count 5500 cells per microliter with 26% lymphocytes and 70% neutrophils | Generalized tonic-clonic seizure | Normal protein, glucose, with five cell counts but was unremarkable for COVID-19 infection | Intravenous phenytoin and levetiracetam, chloroquine, lopinavir-ritonavir | The symptoms of the patient improved with anticonvulsive and antiviral medications. | [38] |
| 60-year-old man | Steroid-responsive encephalopathy | Fever, cough | N.R | Brain CT scan was unremarkable | Generalized slowing, more prominent on the anterior regions with decreased reactivity to acoustic stimuli | Normal blood cell counts, increased D-dimer (96 mg/mL) but normal levels of CRP, fibrinogen and ferritin | Severe encephalopathy, cognitive fluctuations, progressive irritability, confusion and asthenia, severe alteration of consciousness. | Inflammatory findings with mild lymphocytic pleocytosis (18/ul) and moderate increase of CSF protein (696 mg/dL) | Lopinavir/ritonavir hydroxychloroquine, high intravenous steroid treatment (methylprednisolone) | The clinical response to steroid therapy was quite impressive, the clinical conditions of the patient improved | [27] |
| 32-year-old pregnant woman | Generalized tonic-clonic convolution | Fever, chills, unproductive cough and no sore throat | No medical history | N.R | N.R | N.R | Total leukocyte count was 12.3 × 10⁹/L and lymphocyte count was 1.6 × 10⁹/L. Hemoglobin level, liver and renal function tests, and serum lactate dehydrogenase were normal | Myalgia | Hydrocortisone, ribavirin, piperacillin/tazobactam | N.R | [41] |
| Wuhan male | Encephalitis | Fever, shortness of breath | N.R | CT was normal | N.R | N.R | Myalgia, confusion, nuchal rigidity, Kernig sign and Brudzinski sign and extensor plantar response | The cerebrospinal fluid pressure was 220 mmHg, Laboratory tests with CSF showed WBC (0.001 × 10⁹/L), protein (0.27 g/L), ADA (0.17 U/L) and sugar (3.14 mmol/L) contents within normal limits, negative for SARS-CoV-2 | Arbidol and oxygen therapy, mannitol infusion | CSF pressure gradually reduces and the patient’s consciousness gradually improves. | [28] |
| 65-year-old male | Guillain-Barré syndrome (GBS) | Cough, fever and sometimes dyspnea | Type 2 diabetes mellitus | Normal finding except for mild herniation of two | N.R | N.R | White blood cell count 14,700 cells per microliter (neutrophils = 82.7%); Acute progressive symmetric ascending quadriaparesis, | N.P | Hydroxychloroquine, lopinavir, ritonavir, and azithromycin | N.R | [46] |
| Case demographic          | Diagnosis                                      | General sign & symptoms                  | Medical history                                | CT scan of the head | MRI | EEG                              | Laboratory testing                                                                 | CNS & PNS involvement                                                                 | CSF analysis                | Treatment                          | Results                                      | Ref. |
|--------------------------|------------------------------------------------|------------------------------------------|-----------------------------------------------|---------------------|-----|---------------------------------|--------------------------------------------------------------------------------|---------------------------------------------------------------------------------|--------------------------|---------------------------------------------|---------------------------------------------|------|
| A 50-year-old man        | Miller Fisher syndrome                        | Cough, malaise, headache, low back pain, and a fever |                                | N.R     | N.R | N.R                             | intervertebral discs.                                                             | lympoocytes = 10.4%, alanine aminotransferase 35 IU/L; aspartate aminotransferase 47 IU/L; Lymphopenia (1000 cells/ul) and elevated C-reactive protein (2.8 mg/dL), positive to the antibody GD1b-lgG | An opening pressure of 11 cm of H2O, white blood cell count = 0/μL, protein = 80 mg/dL, glucose = 62 mg/dL, with normal cytology | Immunoglobulin and acetaminophen | Resolution of the neurological features, except for residual anosmia and ageusia. | [47] |
| A 39-year-old man         | Polyneuritis Cranialis                        | A low grade fever, diarrhea              | Past medical history was unremarkable        | N.R     | N.R | N.R                             | Normal electrolytes, leukopenia (3100 cells/ul)                                | Ageusia, Bilateral abducens palsy, Areflexia and albuminocytologic dissociation | An opening pressure of 10 cm H2O, white blood cell count = 2/μL, (all monocytes), protein = 62 mg/dL, glucose = 50 mg/dL, with normal cytology | Acetaminophen and Telemedicine | Complete eye movements, complete neurological recovery | [47] |
| A female airline worker in her late fifties | Acute necrotizing hemorrhagic encephalopathy | A 3-day history of cough, fever          | N.R                                            | N.R     | N.R | N.R                             | Hemorrhagic rim enhancing lesions within the bilateral thalami, medial temporal lobes, and subinsular regions | Altered mental status | CSF analysis was limited due to a traumatic lumbar puncture | Intravenous immunoglobulin | N.R | [30] |

N.R: Not reported; NP: Not performed.
alterations [44]. Lechien et al. analyzed a total of 417 mild-to-moderate COVID-19 patients for the olfactory and gustatory dysfunctions. Of 417 patients, 357 patients (85.6%) had olfactory dysfunction which among those, 284 (79.6%) patients showed anosmia, and 73 (20.4%) patients showed hyposmia during the disease course. Furthermore, 12.6% of these patients were phantomic and 32.4% of patients were parosmic. Similar to the previous report, the timing of alteration in sense of smell or taste onset compared to the other symptoms were also examined in this study. The olfactory dysfunction was occurred before (11.8%), after (65.4%) or at the same time as the appearance of other symptoms (22.8%). Moreover, 342 patients (88.8%) reported gustatory dysfunction. However, any significant association was not found between co-morbidities and the development of olfactory or gustatory disorders. It has been estimated that the olfactory dysfunction in 56% of patients will be permanent after resolution of the COVID-19 general symptoms. In 63.0% of patients, the olfactory disorder remained even after other symptoms resolution. Probable reason for lasting these symptoms is infection of both resting and activated horizontal basal cells (HBCs). These reserve stem cells are activated during tissue damages and also express the ACE2 and TMPRSS2 receptors [12]. Guillain–Barré syndrome (GBS) is an acute immune-mediated complication which involves the peripheral nerves and nerve roots and its pathomechanism is similar to an autoimmune disorder [45]. The first case of Guillain–Barré syndrome (GBS) in a patient with COVID-19 was a 65-year-old male with acute progressive symmetric ascending quadriparesis. He had bilateral facial paresis and no urinary and fecal incontinence. Mild hermia of two intervertebral discs was observed in MRI imaging [46]. Although the SARS-CoV-2 mechanism in induction of GBS is not clear, it is suggested that COVID-19 may contribute in the production of antibodies against specific gangliosides which involve in certain forms of GBS [46]. Table 1 summarizes the CNS and PNS manifestations of SARS-CoV-2.

6. The impacts of COVID19 on neurological disorders

The COVID-19 pandemic as an external stressor has several short-term as well as long-term adverse effects on a large groups of people, especially some with underlying diseases such as neurological disorders. Parkinson’s disease (PD) is one of these neurological complication which ethiologically affects dopamine-producing (“dopaminergic”) neurons due to the accumulation of α-synuclein (α-syn) aggregates in a specific area of the brain called substantia nigra [48]. PD is also reported to endanger the respiratory system [49]. The COVID-19 pandemic increases stress among population and exacerbates different motor symptoms, such as tremor, freezing of gait or dyskinesias, [50] and also diminished the efficacy of dopaminergic medication [51–53]. Interestingly, association between COVID-19 pathophysiology and alteration in dopamin synthesis pathway has been hypothesized. It has been demonstrated that Dopa Decarboxylase (DDC), a major enzyme of both dopamine and serotonin synthetic pathways, is significantly co-expressed with ACE2 receptor. On the other hand, SARS-COV virus, the other causin of COVID-19, induces the ACE2 down-regulation which could be consistent with dopamine synthesis alteration [54]. Interestingly, dopamine receptors are expressed in the alveolar epithelial cells and probably dopamine contributes in lung immunity [55]. Although the above mentioned notes about dopamine, ACE2, and COVID-19 are not overt, these evidence put this hypothesis in researcher’s mind which defective expression of the ACE2 and DDC may alter dopamin levels in the blood of patients with COVID-19. Moreover, dysregulation of dopamine may worsen the severity of PD [56]. In addition to the impact of COVID-19 on PD patients, the virus may cause sporadic PD in infected individuals. The Braak hypothesis says that a neuroinvasive virus could enter to the CNS through the nasal cavity and the gastrointestinal tract [57].

Multiple sclerosis (MS) is another neurological disease that COVID-19 infection may threat in individuals with MS. The mortality/morbidity risk in MS patients with COVID-19 who are treated with disease modifying therapies (DMTs), is probably quite moderate to low. Moreover, administration of immunomodulatory drugs in these patients leads to limited lung capacity which increases the risk of COVID-19 related pneumonia [58]. Decision for stopping or continuing the DMT for MS patients infected with COVID-19 depends on individual factors such as disease severity and activity [59]. Moreover, sever complication of COVID-19 infection results from an over-reaction of immune system to the virus [59]. Ramanathan et al. hypothesised that moderate immunosuppression therapy which is taken for MS patients may increase the risk of severe COVID-19 complications [60]. In this line, several trials have been performed to examine the ability of immunosuppressive drugs for mitigating the immune response to the virus [61,62].

7. Conclusion and future prospects

COVID-19 patients may show neurological manifestations such as headache, consciousness disorder, and other pathological signs. The main symptom of SARS-CoV-2 is related to the respiratory system. However it has been suggested that the respiratory manifestation may associated with the virus invasion to the cardio-respiratory center in the brain stem. According to the reports, neurological symptoms in COVID-19 patients are associated with disease severity. Although these neurological manifestation are rare, they can cause serious complications if not diagnosed and managed early. Since neurological manifestation are often non-specific at the early stages of COVID-19 infection, the risk of misdiagnosis or delayed diagnosis will increase. Due to the serious impacts of COVID-19 on the nervous system, more studies are needed to elucidate the long-term effects of SARS-CoV-2 on the nervous system function and it is of interest to shedding light on the exact mechanisms of its neuroinvasion. Moreover, in order to find the neuroinvasive behaviors of SARS-CoV-2, further in vitro and in vivo studies are needed to be performed.

Declarations of competing interest

The authors declare no conflicts of interest.

Acknowledgments

There are no funders to report for this study.

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