COVID-19 Pandemic – Neurological Aspects of the Disease

Hrvoje Budinčević1,2, Dorotea Vidaković2, Hrvoje Jurlina3, Vida Demarin4,5.

1 Stroke and Intensive Care Unit, Department of Neurology, Sveti Duh University Hospital, Zagreb, Croatia
2 Faculty of Medicine, University J. J. Strossmayer, Osijek, Croatia
3 Zagreb County Health Center, Velika Gorica, Croatia
4 Department of Medical Sciences, Croatian Academy of Sciences and Arts, Zagreb, Croatia
5 International Institute for Brain Health, Zagreb, Croatia

ABSTRACT:
With severe acute respiratory syndrome corona virus-2 disease the World is faced with a new pandemic. It has become a global public health concern similar to severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS) outbreaks. The aim of this review is to provide a comprehensive summary of the main clinical and neurological manifestations of this new infectious disease, named Coronavirus disease 2019 (COVID-19). The main clinical manifestations of COVID-19 are related to respiratory system, but neurological symptoms and diseases are also possible due to neuroinvasive potential of the virus. Most COVID-19 cases experience mild clinical symptoms and recover without complications, but 5% of cases need intensive care treatment. The most common neurological symptoms are headache, dizziness, hyposmia and hypogeusia. Neurological diseases which are associated with COVID-19 are stroke, encephalopathy, meningoencephalitis, and Guillain Barre syndrome. Preventive measures are the most effective for containment of COVID-19. These measures include isolation modalities with physical distancing, cover coughs or sneezes, and frequent handwashing with soap and water or using hand sanitizers, and avoiding public gatherings. Unfortunately, no specific antiviral medication or vaccine is currently available. The new virus enters the cell through a cellular receptor angiotensin-converting enzyme-2, the questions regarding use of the renin-angiotensin-aldosterone system inhibitors. According to the recent data most professional societies recommended the use of these medications.

KEYWORDS: Coronaviruses, COVID-19, neurological, nervous system.

SAŽETAK:
COVID-19 pandemija – neurološki aspekti bolesti
Bolest uzrokovana virusom teškog akutnog respiratornog sindroma 2 dovела je do pandemije. Ova globalna javno-zdravstvena prijetnja slična je prethodnim epidemijama sindroma teškog respiratornog sindroma (SARS) i bliskoistočnog respiratornog sindroma (MERS). Cilj ovog rada je pružiti pregled vodećih kliničkih i neuroloških manifestacija ove nove zarazne bolesti, nazvane Coronavirusna bolest 2019 (COVID-19). Glavne kliničke manifestacije ove bolesti povezane su s dišnim sustavom, ali mogući su neurološki simptomi i bolesti zbog neuroinazivnog potencijala virusa. Većina slučajeva COVID-19 ima blaje kliničke simptome i oporavljaju se bez komplikacija, ali 5% slučajeva zahtijeva intenzivno liječenje. Najčešći neurološki simptomi su glavobolja, vrtoglavica, hiposmija i hipogeusija. Neurološke bolesti povezane s COVID-19 su možani udar, encefalopatija, meningoencefalitis i akutni poliradikuloneuritis (Guillain Barre-ov sindrom). Preventivne mjere naručenke i bolesti su za suzbijanje COVID-19. Te mjere uključuju metode izolacije i tjelesnog distanciranja, metode spriječavanja širenja bolesti kapličnim putem (pokrivanje lica pri kašljanju i kihanju) te učestalo pranje ruku sapunom i vodom ili korištenje sredstva za dezinfekciju ruku, kao i izbjegavanje javnih skupova. Nažalost, ova
Infection within CoVs (especially SARS-COV, MERS-CoV and SARS-CoV-2) lead to respiratory, enteric, hepatic and neurologic diseases and MERS-CoV. The basic reproduction number is 2.2. A symptomatic individual may transmit the virus. The most common source of the infection and potentially by fecal-oral transmission is now considered the main form of transmission of SARS-CoV2. The pangolin is the probable animal host for MERS-CoV by camel and SARS-CoV by civet and MERS-CoV by camel. The probable animal host of SARS-CoV2 is pangolin. Currently, human-to-human transmission is now considered the main form of transmission. The virus is a RNA (26 to 32KB genome) type with a recombination rate up to 25% and covered by a crown of glycoproteins that can mutate frequently.

All human CoVs have zoonotic origins. The natural hosts for all known CoVs are most likely bats. The virus is probably transmitted by another animal host, such as SARS-CoV by civet and MERS-CoV by camel. The probable animal host of SARS-CoV2 is pangolin. Currently, human-to-human transmission is now considered the main form of transmission. SARS-CoV-2 (sized 0.125um) is transmitted predominantly by inhalation via respiratory droplet, direct or indirect contact and potentially by fecal-oral. Symptomatic individuals are the most common source of the infection. However, asymptomatic individuals may transmit the virus. Basic reproduction number is 2.2, what is more contagious than SARS and MERS. The mean incubation period is 5 days (2 to 14 days). CoVs can cause multiple systemic infections that can lead to respiratory, enteric, hepatic and neurologic diseases. Infection within CoVs (especially SARS-COV, MERS-CoV and SARS-CoV-2) may lead to severe clinical symptoms with high mortality. SARS viruses infect the cells of pulmonary alveolus, causing acute diffuse alveolar damage, edema and inflammation which can evolve to acute respiratory distress syndrome (ARDS) in adults. These viruses can be functionally inactivated with the use of ethanol (60%), ether (75%) and chlorine-containing disinfectants.

**Introduction**

The World is faced with a new pandemic with severe acute respiratory syndrome corona virus 2 (SARS-CoV-2) causing coronavirus disease 2019 (COVID-19). The global public health concern is on high level since last two outbreaks caused by severe acute respiratory syndrome (SARS) in 2003 and Middle East respiratory syndrome (MERS) in 2012. Due to a great threat for public health safety the World Health Organization (WHO) on March 11, 2020 declared a pandemic for COVID-19. In Wuhan, China, the first patients were discovered on December 1st, 2019. The pandemic quickly and widely spread worldwide. On May 19, 2020 there were 4696849 confirmed cases of COVID-19, including 315131 deaths. In the same period, Croatia had 2226 confirmed cases, including 95 deaths. The aim of this review is to provide a comprehensive summary of the main clinical and neurological manifestations of this new infectious disease named Coronavirus disease 2019 (COVID-19).

**Coronaviruses**

Corona viruses (CoV) family is a class of enveloped, positive sense single stranded RNA viruses having extensive range of natural roots. Genotypically and serologically coronaviruses are divided in four subfamilies: alpha, beta, gamma, and delta. Similarly, to SARS-CoV and MERS-CoV, the SARS-CoV-2 belongs to the beta-CoV subfamily. The virus is a RNA (26 to 32KB genome) type with a recombination rate up to 25% and covered by a crown of glycoproteins that can mutate frequently. All human CoVs have zoonotic origins. The natural hosts for all known CoVs are most likely bats. The virus is probably transmitted by another animal host, such as SARS-CoV by civet and MERS-CoV by camel. The probable animal host of SARS-CoV2 is pangolin. Currently, human-to-human transmission is now considered the main form of transmission. SARS-CoV-2 (sized 0.125um) is transmitted predominantly by inhalation via respiratory droplet, direct or indirect contact and potentially by fecal-oral. Symptomatic individuals are the most common source of the infection. However, asymptomatic individuals may transmit the virus. Basic reproduction number is 2.2, what is more contagious than SARS and MERS. The mean incubation period is 5 days (2 to 14 days). CoVs can cause multiple systemic infections that can lead to respiratory, enteric, hepatic and neurologic diseases. Infection within CoVs (especially SARS-COV, MERS-CoV and SARS-CoV-2) may lead to severe clinical symptoms with high mortality. SARS viruses infect the cells of pulmonary alveolus, causing acute diffuse alveolar damage, edema and inflammation which can evolve to acute respiratory distress syndrome (ARDS) in adults. These viruses can be functionally inactivated with the use of ethanol (60%), ether (75%) and chlorine-containing disinfectants.

**Neuroinvasive potential of coronaviruses**

Despite known respiratory tract infection, coronaviruses may also invade the central nervous system, e.g. human CoV-OC43 has been associated with fatal encephalitis in children. Neuroinvasive character of beta-CoVs are reported in SARS-CoV and MERS-CoV. Due to high similarity showed between SARS-CoV and SARS-CoV-2, it is likely that potential neuroinvasion of SARS-2 plays an important role in the acute respiratory failure of COVID-19 patients as well.

The entry of SARS-CoV host cells is mediated by a cellular receptor angiotensin-converting enzyme 2 (ACE2). The MERS-CoV enters the human cells mainly via dipeptidyl peptidase 4 (DPP4). Receptors for ACE2 is expressed in human airway epithelia, lung parenchyma, vascular endothelia, kidney cells and small intestine cells. The DPP4 is present in the lower respiratory tract, kidney, small intestine, liver and the cells of immune system. The previous reports showed that the expression level of ACE2 or DPP4 are very low under normal conditions. ACE2 expression is widespread in the brain (on neurons and glial cells), not only in the cardiorespiratory centers in medulla, but also in the striatum. SARS-CoV infection, through binding of viral S protein to ACE2, seems to reduce the receptor expression. ACE2, a homologue of ACE, is an integral part of the cell membrane protein with catalytic domain on the extracellular surface exposed to vasoactive peptides. ACE2 converts Ang II to Ang 1-7 – with vasodilatory and antifibrotic action when it activates Mas receptor. ACE2 expression in heart, type II alveolar cells (AT2), capillary endothelium and enterocytes demonstrates an essential role in the cardiovascular and immune system, basically in the development of hypertension and diabetes mellitus complications. SARS-CoV-2 penetrates the cell through ACE2, but necessities type II transmembrane serine protease (TMPRSS2) for effective priming of viral spike (S) protein. The binding of S protein to ACE2 allows proteolytic digestion by TMPRSS2 – which enables viral and cell membrane fusion and later release of viral particles. Recent two independent studies with patients with heart failure
found that the plasma concentrations of ACE2 were higher in men than in women, but neither an ACE inhibitor nor an ARB was associated with a higher plasma ACE2 concentrations 30. Experimental studies using transgenic mice revealed either SARS-CoV or MERS-CoV could enter the brain via olfactory nerves and then rapidly spread to thalamus and brainstem31,32. Detection of high viral load in the brainstem after SARS-CoV infection is indicative of the spreading of the infection from the respiratory tract to the central nervous system via vagal nerve to ambiguous and solitary tract in the brainstem33. The involvement may also suggest that the respiratory center contributes to the severe respiratory distress caused by COVID-1934. Recently there was a report of a patient with COVID-19 with the loss of involuntary breathing process – probably Ondine’s course syndrome35. Since the SARS-CoV-2 shares similarities with SARS-CoV and as a member of coronaviruses family it is likely to possess similar potential for neuroinvasion, especially medullary neurons causing headache, nausea, and vomiting36. The coronavirus RNA can be detected in the cerebrospinal fluid34,35. The involvement of CNS is probably caused by focal meningitis/encephalitis affecting rhinal cortex, gustatory cortex or appropriate subcortical ascending/descending tracts35. Other potential entry points are peripheral nerve terminals that gain access to the CNS via a synapse connection route – trans-synaptic transfer36. The peripheral nerve system is targeted by SARS-Cov-2, in particular nerves I, VII, IX, X 35. Hyposmia which is caused by a direct contact and interaction of the virus with gustatory receptors and olfactory receptor cells35.

Clinical presentation
Generally, coronaviruses are responsible for 5-10% of acute respiratory infections40. The SARS-CoV-2 may present as a mild, moderate and severe disease41. The disease is asymptomatic or milder in children and young adults42. The symptomatic adult form has increasing severity with age, health care workers are notable exception43. COVID-19 can have a clinical presentation similar to influenza, typically with fatigue, fever and non-productive/dry cough44. Other symptoms include dyspepsia, hemoptysis, sore throat and leg pain45. Dyspnea and/or hypoxemia occurs in patients with severe course after the first week46. Diarrhea has been reported as an initial symptom in fewer cases47. Critical cases were rapidly progressive with complications such as ARDS, septic shock, refractory metabolic acidosis and coagulation dysfunction48. SARS main clinical manifestations were fever, chills, dry cough and difficulty breathing49. Severe cases led to respiratory failure (ARDS 20%) and death49. MERS patients were usually presented with pneumonia related symptoms such as fever, myalgia, cough and dyspnea45. Severe cases led to ARDS (5%), septic shock and multiorgan failure, acute renal failure and death45. Most COVID-19 cases (80%) experience mild clinical symptoms and recover without complications, 5% of cases need intensive care due to pneumonia and respiratory failure developing in up to 14 days 40. The most severe cases require prolonged duration of care (more than 14 days)35. Age is the most important risk factor; there is a progressive rise of cases after 50 years of age 41. Registered lethality varies between European countries ranging from 1.5% in Germany to over 10% in Italy 4. Risk factors associated with more severe cases are: arterial hypertension, cardiovascular and cerebrovascular disease, diabetes and immunosuppression42. Table 1. shows risk factors for COVID-19.

Chen T et al. evaluated 113 deceased patients with COVID-19 and found predominance of male sex (73%), median age of 68 years, chronic hypertension and cardiovascular comorbidities (48%), with leukocytosis (50%) and lymphopenia (91%) and the most common complication was ARDS (100%)43. Du Y et al. have analyzed fatal cases of COVID-19 from Wuhan, China44. They showed that the most of 85 cases were males over 50 years of age with noncommunicable chronic diseases (arterial hypertension, diabetes and coronary heart disease), and the majority of patients died of multiple organ failure45. Poor prognosis was associated with early onset of shortness of breath and eosinophilia46. The most common complications included respiratory failure (94.1%), shock (81.2%), ARDS (74.1%), and arrhythmias (60%). The reported case fatality rate is 1.8 to 3.4%44. Laboratory findings includes lymphopenia (83%), thrombocytopoenia (36%), neutropenia (34%), elevated D-dimer levels (47%) and prothrombine time, lactate dehydrogenase (41%), C-reactive protein (36%)14,15. As in SARS and MERS, most COVID-19 patients have a characteristic ground glass appearance on chest CT scans and bilateral patchy shadowing in more than 50% of patients16.

Neurological manifestations
During a pandemic neurologic manifestations might be overlooked47. On the other hand, the COVID-19 pandemic caused the reduction of neurology services, especially showed through stroke care where there was a reduction in the number of hospital admissions46. Neurological manifestations may be caused by direct or indirect (para-infectious) mechanisms of invasion by CoVs48. CoVs infections have been associated with neurological manifestations such as: febrile seizures, convulsions, change in mental status and encephalitis4. Neurological symptoms were rarely reported in the previous SARS and MERS outbreak49. The high number of patients with COVID-19, which may have the presence of the virus in the CNS, require monitoring for early and late onset neurological symptoms, including neurological and neurodegenerative disorders50,51. In SARS outbreak the reported neurological manifestations include axonopathic polyneuropathy, encephalitis, myopathy, rhabdomyolysis and acute ischemic stroke51. The reported neurological symptoms within MERS outbreak include disturbance of consciousness, Bicker-
Risk factors for COVID-19

| Risk Factor                  |
|-----------------------------|
| Age (>65 years)             |
| Current smoker              |
| Hypertension                |
| Diabetes                    |
| Coronary heart disease      |
| Atrial fibrillation         |
| Chronic obstructive lung disease |
| Chronic kidney disease      |
| Cancer                      |
| Obesity (BMI>30)            |
| Immunosuppression           |

staff's encephalitis overlapping with Guillain-Barre syndrome, ischemic stroke, vasculopathy, ADEM, infectious neuropathy, intensive care acquired weakness and seizures. A greater concern than direct invasion of the CNS may be para-infectious neurological diseases such as GBS, transverse myelitis and ADEM – such as in the ZIKA virus epidemic in 2015-2016. However, neurological manifestations of COVID-19 have not been studied appropriately yet. CNS involvement and neurological manifestations are probably present particularly in patients with severe illness. The most commonly reported preexisting neurological diseases in COVID-19 patients were cerebrovascular diseases, nervous system diseases, prior stroke, dementia and Parkinson's disease. According to the study from Wuhan which showed that 36.4% of patients had neurological symptoms, and these were more frequent with severe disease. The most common reported symptoms identified were headache (8.34%) and dizziness (16.8%), while anosmia occurred in 5.1% and hypogeusia in 5.6% cases. However, the study of Lechien et al. found that olfactory and gustatory dysfunctions were found in more than 85% of patients with mild to moderate COVID-19. In the study female patients were particularly affected by olfactory and gustatory dysfunctions. Therefore, the sudden onset of anosmia or ageusia should be recognized as a symptom of COVID-19. Other reported neurological symptoms were: nausea, fatigue, myalgia, ataxia, deficit in visual field, nevralgia and seizures. Intracranial infection related symptoms included headache, seizures, disturbance of consciousness. The recent retrospective study by Lu et al. concluded that there is no evidence that suggesting an additional risk of acute symptomatic seizures in people with COVID-19. A French study reported that COVID-19 might be presented as encephalopathy, prominent agitation, confusion or corticospinal tracts signs. The study by Herman et al. found that 8% of hospitalized COVID-19 patients had pre-existing neurological illnesses. Secondary neurological complication rate were between 6 and 36.4%. Cases of encephalopathy, meningoencephalitis, and Guillain Barre syndrome were associated with COVID-19. One of first reported cases was a COVID-19 patient with acute necrotizing encephalopathy. The study of Chen et al. reported up to 20% hypoxic/ischemic encephalopathy. Patients with cerebrovascular diseases are prone to develop COVID-19 with severe respiratory complications or multiple organ failure. The same study from Wuhan which found 36% (from 216 cases) of neurological manifestation and 2.8% of patients suffered a stroke (6 cases). Acute stroke was more common among 88 patients with severe COVID-19 infections (5.7%, 4 ischemic strokes, 1 intracerebral hemorrhage) than in non-severe infections (0.8%, 1 ischemic stroke). Another retrospective study of data from the COVID-19 outbreak in Wuhan showed the incidence of stroke of 5% (11 cases: 5 had large artery disease, 3 had cardioembolic stroke, and 3 had small artery disease). Oxley et al. and Beyrouti et al. reported the case series of large vessel occlusion strokes in COVID-19 patients. The associated of COVID-19 and development of ischemic stroke is linked to prothrombotic state causing venous and arterial thromboembolism. Causes of stroke were associated with raised levels of D-dimer, exaggerated systemic inflammation, a "cytokine storm" (a hallmark of severe disease) and cardioembolism (from virus related cardiac injury). The presumed incidence of stroke in patients with COVID-19 is 4.9%, and the possibility that COVID-19 increases the risk of stroke is 7.82 folds within first three days after the onset of respiratory tract infection. Health care providers engaged in acute stroke care are at risk of acquiring COVID-19 from stroke patients with COVID-19. The recent pooled analysis of four studies by Aggarwal et al. showed that cerebrovascular disease to be associated with 2.5 fold increased disease severity in patients with COVID-19. There was no significant association of stroke mortality in patients with COVID-19 infection. Nevertheless, it was found that there was a decrease of 39% in the numbers of patients who received evaluations (neuroimaging) for acute stroke in United States of America during COVID-19 pandemic. Conversely, there could also be associated factors which could have reduced stroke incidence, such as air pollution, many countries reported reduction in air pollution. The assumption that air pollution conditions facilitate the spread of a virus was shown during SARS outbreak in 2002 and during COVID-19, but this hypothesis still has to be validated. Effect of social distancing measures and anxiety may contribute for disease development. Autopsy reports of COVID-19 patients have revealed brain edema and partial neuronal degeneration in deceased patients. The study of Helms et al. showed unexplained encephalopathic features in patients with COVID-19 who had MRI performed. The perfusion abnormalities were noted in 11 patients: leptomeningeal enhancement in 8 patients, and 3 patients had ischemic stroke on MRI. This review covers mostly short-term effects of COVID-19, but we should be aware of the long-term effects that SARS-COV-2 could produce regarding other or chronic neurological conse-
quences (e.g. cognitive impairment, ADEM, etc.)

**Treatment options**

Isolation remains the most effective measure for containment of COVID-19. Preventive measures include isolation modalities with physical distancing, cover coughs or sneezes, and frequent handwashing with soap and water or using hand sanitizers, and avoiding public gathering. No specific antiviral medication or vaccine is currently available. Treatment includes symptomatic care with oxygen therapy. Researchers are currently investigating specific treatments for COVID-19. The treatments which are being investigated are shown in the table.

The question was raised regarding the safe usage of renin-angiotensin-aldosterone system (RAAS) inhibitors during COVID-19 pandemic. RAAS inhibitors include ACE inhibitors (ACE-I) and angiotensin-receptor blockers (ARB) which increase expression of ACE2. The use of ACE-I and ARB was more frequent among patients with COVID-19 than controls because of their higher prevalence of cardiovascular disease. However, there was no evidence that these medications affect the risk of COVID-19, despite the previous concerns about possibility that these drugs could predispose individuals to severe COVID-19. A recent study confirmed that outpatient use of RAAS inhibitors does not increase the risk of COVID-19 requiring admission to hospital, including most severe cases.

The study of Khera et al. showed that the use of RAAS inhibitors was not associated with the risk of hospitalization or mortality among patients infected with SARS-COV-2. Interestingly, the same study showed that the risk of hospitalization was nearly 40% lower in patients who used ACE-I. The study of Mehra et al. which included 8900 COVID-19 patients showed that the use of either ACE-I or statins was associated with better survival. Most professional societies recommend the continuation of the use of these medications because their positive effect on the cardiovascular system.

In summary, COVID-19 caused higher infection and mortality rates than SARS and MERS, mainly caused by respiratory failure. As in the previous two outbreaks (SARS and MERS), the SARS-CoV-2 shows neuroinvasive potential with various neurological manifestations. We should be aware of the short- and long-term neurological consequences of this pandemic. Unfortunately, the treatment options are still only symptomatic. As far as preventive measures are concerned isolation is the most powerful option for containment of COVID-19. Specific therapies are being evaluating in clinical trials. Additional investigations are warranted in order to evaluate the impact of the development of neurological manifestations of COVID-19.

| Mechanism of action       | Examples                                                                 |
|---------------------------|--------------------------------------------------------------------------|
| Viral entry inhibitors    | 1. Chloroquine and hydroxychloroquine – antimalarials                   |
|                           | 2. APNO1 – recombinant human ACE2 protein                                 |
|                           | 3. Leroninab (PRO 140) – humanized IgG4 monoclonal antibody against CCR5 receptors |
| Viral replication inhibitors | 1. Remdesivir and Favipiravir – nucleotide analogs                        |
|                           | 2. Lopinavir-Ritonavir – protease inhibitors                             |
|                           | 3. Camostat (FOY-305) and Nafamostat mesilate – serine protease inhibitor |
|                           | 4. Umifenovir – membrane fusion inhibitor of influenza virus             |
|                           | (available in China and Russia)                                         |
|                           | 5. 3Clpro (Mpro) – protease of beta coronaviruses                        |
| Vaccine                   | 1. S-trimer                                                              |
|                           | 2. Nucleic Acid Vaccines                                                 |
|                           | 3. mRNA vaccines                                                         |
| Miscellaneous             | 1. Azithromycin                                                          |
|                           | 2. Convalescent plasma                                                   |
|                           | 3. Tocilizumab – anti human IL-6 receptor                                |
|                           | 4. Steroids                                                              |

Summary

In summary, COVID-19 caused higher infection and mortality rates than SARS and MERS, mainly caused by respiratory failure. As in the previous two outbreaks (SARS and MERS), the SARS-CoV-2 shows neuroinvasive potential with various neurological manifestations. We should be aware of the short- and long-term neurological consequences of this pandemic. Unfortunately, the treatment options are still only symptomatic. As far as preventive measures are concerned isolation is the most powerful option for containment of COVID-19. Specific therapies are being evaluating in clinical trials. Additional investigations are warranted in order to evaluate the impact of the development of neurological manifestations of COVID-19.
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