COVID-19 Pandemic – Neurological Aspects of the Disease

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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 dovela 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 neuroinvazivnog potencijala virusa. Većina slučajeva COVID-19 ima blage kliničke simptome i oporavlja se bez komplikacija, ali 5% slučajeva zahtijeva intenzivno liječenje. Najčešći neurološki simptomi su glavobolja, vrtoglavica, hiposmija i hipogeuzija. Neurološke bolesti povezane s COVID-19 su moždani udar, encefalopatija, meningoencefalitis i akutni poliradikuloneuritis (Guillain Barre-ov sindrom). Preventivne mjere najučinkovitije su za suzbijanje COVID-19. Te mjere uključuju metode izolacije i tjelesnog distanciranja, metode sprječavanja širenja bolesti kapljičnim 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

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bolest nema specifičnih antivirusnih lijekova ili cjepivo. Novi virus ulazi u stanicu putem receptora za angiotenzin konvertirajući enzim 2, radi čega je u znanstvenoj zajednici postavljeno pitanja uporabe inhibitora renin-angiotenzin-aldosteronskog sustava. Prema najnovijim podacima većina profesionalnih društava preporučila je nastavak uporabe inhibitora renin-angiotenzin-aldosteronskog sustava.

Ključne riječi: : koronavirusi, COVID-19, neurologija, živčani sustav

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)[1]. 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[2]. 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[3]. 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[4].
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[5]. Genotypically and serologically coronaviruses are divided in four subfamilies: alpha, beta, gamma, and delta[5-7]. Similarly, to SARS-CoV and MERS-CoV, the SARS-CoV-2 belongs to the beta-CoV subfamily[2,5,8]. 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[9,10].
All human CoVs have zoonotic origins [11]. The natural hosts for all known CoVs are most likely bats[11]. The virus is probably transmitted by another animal host, such as SARS-CoV by civet and MERS-CoV by camel[8]. The probable animal host of SARS-CoV2 is pangolin[12]. Currently, human-to-human transmission is now considered the main form of transmission[13]. SARS-CoV-2 (sized 0.125um) is transmitted predominantly by inhalation via respiratory droplet, direct or indirect contact and potentially by fecal-oral[14]. Symptomatic individuals are the most common source of the infection[14]. However, asymptomatic individual may transmit the virus[14,15] . Basic reproduction number is 2.2 [13], what is more contagious than SARS and MERS[16]. The mean incubation period is 5 days (2 to 14 days)[17-19] . CoVs can cause multiple systemic infections that can lead to respiratory, enteric, hepatic and neurologic diseases[14]. Infection within CoVs (especially SARS-COV, MERS-CoV and SARS-CoV-2) may lead to severe clinical symptoms with high mortality[20] . 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[21]. These viruses can be functionally inactivated with the use of ethanol (60%), ether (75%) and chlorine-containing disinfectants[14].

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[22]. Neuroinvasive character of beta-CoVs are reported in SARS-CoV and MERS-CoV[23]. 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[23].
The entry of SARS-CoV host cells is mediated by a cellular receptor angiotensin-converting enzyme 2 (ACE2)[23]. The MERS-CoV enters the human cells mainly via dipeptidyl peptidase 4 (DPPS4)[23]. Receptors for ACE2 is expressed in human airway epithelia, lung parenchyma, vascular endothelia, kidney cells and small intestine cells[23]. The DPP4 is present in the lower respiratory tract, kidney, small intestine, liver and the cells of immune system[23]. The previous reports showed that the expression level of ACE2 or DDP4 are very low under normal conditions[24]. 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[25]. SARS-CoV infection, through binding of viral S protein to ACE2, seems to reduce the receptor expression[26,27]. 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[26]. ACE2 converts Ang II to Ang 1-7 – with vasodilatory and antifibrotic action when it activates Mas receptor[26]. 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[26]. SARS-CoV-2 penetrates the cell through ACE2, but necessities type II transmembrane serine protease (TMPRSS2) for effective priming of viral spike (S) protein[26]. 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[26,28,29].
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 brainstem[31,32]. 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 brainstem[23]. The involvement may also suggest that the respiratory center contributes to the severe respiratory distress caused by COVID-19[33]. Recently there was a report of a patient with COVID-19 with the loss of involuntary breathing process – probably Ondine's course syndrome[23]. Since the SARS-Co-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 vomiting[23]. The coronavirus RNA can be detected in the cerebrospinal fluid[34,35]. The involvement of CNS is probably caused by focal meningitis/encephalitis affecting rhinal cortex, gustatory cortex or appropriate subcortical ascending /descending tracts[35].

Other potential entry points are peripheral nerve terminals that gain access to the CNS via a synapse connection route – trans-synaptic transfer[23]. 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 cells[35].

Clinical presentation

Generally, coronaviruses are responsible for 5-10% of acute respiratory infections[36]. The SARS-CoV-2 may present as a mild, moderate and severe disease[14]. The disease is asymptomatic or milder in children and young adults[33]. The symptomatic adult form has increasing severity with age, health care workers are notable exception[33].

COVID-19 can have a clinical presentation similar to influenza, typically with fatigue, fever and non-productive/dry cough[19]. Other symptoms include dyspnea, hemoptysis, sore throat and leg pain[2,37]. Dyspnea and/or hypoxemia occurs in patients with severe course after the first week[38]. Diarrhea has been reported as an initial symptom in fewer cases[33]. Critical cases were rapidly progressive with complications such as ARDS, septic shock, refractory metabolic acidosis and coagulation dysfunction[38]. SARS main clinical manifestations were fever, chills, dry cough and difficulty breathing[39]. Severe cases led to respiratory failure (ARDS 20%) and death[39]. MERS patients were usually presented with pneumonia related symptoms such as fever, myalgia, cough and dyspnea[40]. Severe cases led to ARDS (5%), septic shock and multiorgan failure, acute renal failure and death[40]. 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)[33]. 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 immunosuppression[42]. 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, China[44]. 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 failure[44]. Poor prognosis was associated with early onset of shortness of breath and eosinophilopenia[44]. 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%), thrombocytopenia (36%), neutropenia (34%), elevated D-dimer levels (47%) and prothrombine time, lactate dehidrogenase (41%), C-reactive protein (36%)[14,19]. 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 patients[10].

Neurological manifestations

During a pandemic neurologic manifestations might be overlooked[45]. 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 admissions[46]. Neurological manifestations may be caused by direct or indirect (para-infectious) mechanisms of invasion by CoVs[45]. CoVs infections have been associated with neurological manifestations such as: febrile seizures, convulsions, change in mental status and encephalitis[2]. Neurological symptoms were rarely reported in the previous SARS and MERS outbreak[47]. 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 disorders[48,49]. In SARS outbreak the reported neurological manifestations include axonopathic polyneuropathy, encephalitis, myopathy, rhabdomyolysis and acute ischemic stroke[50]. The reported neurological symptoms within MERS outbreak include disturbance of consciousness, Bicker-

Risk factors for COVID-19
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[51]. 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[45]. However, neurological manifestations of COVID-19 have not been studied appropriately yet[2]. CNS involvement and neurological manifestations are probably present particularly in patients with severe illness[2,52]. The most commonly reported preexisting neurological diseases in COVID-19 patients were cerebrovascular diseases, nervous system diseases, prior stroke, dementia and Parkinson's disease[53]. According to the study from Wuhan which showed that 36.4% of patients had neurological symptoms, and these were more frequent with severe disease[52]. The most common reported symptoms identified were headache (8-34%) and dizziness (16,8%), while anosmia occurred in 5.1% and hypoageusia in 5.6% cases[38]. 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[54]. In the study female patients were particularly affected by olfactory and gustatory dysfunctions[54]. Therefore, the sudden onset of anosmia or ageusia should be recognized as a symptom of COVID-19[54]. Other reported neurological symptoms were: nausea, fatigue, myalgia, ataxia, deficit in visual field, neuralgia and seizures[38,46,52,55,56]. Intracranial infection related symptoms included headache, seizures, disturbance of consciousness[38,52]. 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[57]. A French study reported that COVID-19 might be presented as encephalopathy, prominent agitation, confusion or corticospinal tracts signs[58].

The study by Herman et al. found that 8% of hospitalized COVID-19 patients had pre-existing neurological illnesses[53]. Secondary neurological complication rate were between 6 and 36.4%[53]. Cases of encephalopathy, meningoencephalitis, and Guillain Barre syndrome are associated with COVID-19[56]. One of first reported cases was a COVID-19 patient with acute necrotizing encephalopathy[52]. The study of Chen et al. reported up to 20% hypoxic/ischemic encephalopathy[43].

Patients with cerebrovascular diseases are prone to develop COVID-19 with severe respiratory complications or multiple organ failure[43]. The same study from Wuhan which found 36 % (from 216 cases) of neurological manifestation and 2.8 % of patients suffered a stroke (6 cases)[52]. 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)[52]. 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)[59]. Oxley et al. and Beyrouti et al. reported the case series of large vessel occlusion strokes in COVID-19 patients [59-60]. The associated of COVID-19 and development of ischemic stroke is linked to prothrombotic state causing venous and arterial thromboembolism and elevated d-dimer levels[61-63]. 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)[46,62]. 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[61].

Health care providers engaged in acute stroke care are at risk of acquiring COVID-19 from stroke patients with COVID-19[64]. 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[64]. There was no significant association of stroke mortality in patients with COVID-19 infection[64]. 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[65].

Conversely, there could also be associated factors which could have reduced stroke incidence, such as air pollution, many countries reported reduction in air pollution 46. 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[66,67]. Effect of social distancing measures and anxiety may contribute for disease development[59].

Autopsy reports of COVID-19 patients have revealed brain edema and partial neuronal degeneration in deceased patients[68]. 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[58].

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-

Potential treatment options for COVID-19	
Mechanism of action	Examples
Viral entry inhibitors	1. Chlorquine and hydroxychloroquine – antimalarials 2. APN01 – recombinant human ACE2 protein 3. Leronimab (PRO 140) – humanized IgG4 monoclonal antibody against CCR5 receptors
Viral replication inhibitors	1. Remdesivir and Favirapir – 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

quences (e.g. cognitive impairment, ADEM, etc.)[45].

Treatment options

Isolation remains the most effective measure for containment of COVID-19[14]. 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[14].

No specific antiviral medication or vaccine is currently available[3]. Treatment includes symptomatic care with oxygen therapy 14. Researchers are currently investigating specific treatments for COVID-19. The treatments which are being investigated are shown in the table 2 [3,29,69,70].

The question was raised regarding the safe usage of renin-angiotensin-aldosterone system (RAAS) inhibitors during COVID-19 pandemic[71]. RAAS inhibitors include ACE inhibitors (ACE-I) and angiotensin-receptor blockers (ARB) which increase expression of ACE2[72]. 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[73]. 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[73,74]. 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[71]. 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[75]. Interestingly, the same study showed that the risk of hospitalization was nearly 40% lower in patients who used ACE-I[75]. 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[76]. Most professional societies recommend the continuation of the use of these medications because their positive effect on the cardiovascular system[26,73].

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.

Literature:

1. Gutierrez-Ortiz C, Mendez A, Rodrigo-Rey S, et al. Miller Fisher Syndrome and polyneuritis cranialis in COVID-19. Neurology 2020.
2. Asadi-Pooya AA, Simani L. Central nervous system manifestations of COVID-19: A systematic review. Journal of the neurological sciences 2020;413:116832.
3. Nicastri E, Petrosillo N, Bartoli TA, et al. National Institute for the Infectious Diseases "L. Spallanzani", IRCCS. Recommendations for COVID-19 clinical management. Infectious disease reports 2020;12:8543.
4. World Health Organszation - internet page. (Accessed 20.5.2020, at https://covid19.who.int/.)
5. Jin Y, Yang H, Ji W, et al. Virology, Epidemiology, Pathogenesis, and Control of COVID-19. Viruses 2020;12.
6. Weiss SR, Leibowitz JL. Coronavirus pathogenesis. Advances in virus research 2011;81:85-164.
7. de Wilde AH, Snijder EJ, Kikkert M, van Hemert MJ. Host Factors in Coronavirus Replication. Current topics in microbiology and immunology 2018;419:1-42.
8. Yi Y, Lagniton PNP, Ye S, Li E, Xu RH. COVID-19: what has been learned and to be learned about the novel coronavirus disease. International journal of biological sciences 2020;16:1753-66.
9. Wrapp D, Wang N, Corbett KS, et al. Cryo-EM structure of the 2019-nCoV spike in the prefusion conformation. Science 2020;367:1260-3.
10. Zhou P, Yang XL, Wang XG, et al. A pneumonia outbreak associated with a new coronavirus of probable bat origin. Nature 2020;579:270-3.
11. Vijaykrishna D, Smith GJ, Zhang JX, Peiris JS, Chen H, Guan Y. Evolutionary insights into the ecology of coronaviruses. Journal of virology 2007;81:4012-20.
12. Zhang T, Wu Q, Zhang Z. Probable Pangolin Origin of SARS-CoV-2 Associated with the COVID-19 Outbreak. Current biology : CB 2020;30:1346-51 e2.
13. Cascella M, Rajnik M, Cuomo A, Dulebohn SC, Di Napoli R. Features, Evaluation and Treatment Coronavirus (COVID-19). In: StatPearls. Treasure Island (FL); 2020.
14. Hassan SA, Sheikh FN, Jamal S, Ezeh JK, Akhtar A. Coronavirus (COVID-19): A Review of Clinical Features, Diagnosis, and Treatment. Cureus 2020;12:e7355.
15. Hoehl S, Rabenau H, Berger A, et al. Evidence of SARS-CoV-2 Infection in Returning Travelers from Wuhan, China. The New England journal of medicine 2020;382:1278-80.
16. Tang B, Bragazzi NL, Li Q, Tang S, Xiao Y, Wu J. An updated estimation of the risk of transmission of the novel coronavirus (2019-nCov). Infectious Disease Modelling 2020;5:248-55.
17. Rothan HA, Byrareddy SN. The epidemiology and pathogenesis of coronavirus disease (COVID-19) outbreak. Journal of autoimmunity 2020;109:102433.
18. Lauer SA, Grantz KH, Bi Q, et al. The Incubation Period of Coronavirus Disease 2019 (COVID-19) From Publicly Reported Confirmed Cases: Estimation and Application. Annals of internal medicine 2020;172:577-82.
19. Guan WJ, Ni ZY, Hu Y, et al. Clinical Characteristics of Coronavirus Disease 2019 in China. The New England journal of medicine 2020;382:1708-20.
20. Zhao M, Wang M, Zhang J, et al. Advances in the relationship between coronavirus infection and cardiovascular diseases. Biomedicine & pharmacotherapy = Biomedecine & pharmacotherapie 2020;127:110230.
21. Chen N, Zhou M, Dong X, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet 2020;395:507-13.
22. Arabi YM, Harthi A, Hussein J, et al. Severe neurologic syndrome associated with Middle East respiratory syndrome corona virus (MERS-CoV). Infection 2015;43:495-501.
23. Li YC, Bai WZ, Hashikawa T. The neuroinvasive potential of SARS-CoV2 may play a role in the respiratory failure of COVID-19 patients. Journal of medical virology 2020.
24. Yashavantha Rao HC, Jayabaskaran C. The emergence of a novel coronavirus (SARS-CoV-2) disease and their neuroinvasive propensity may affect in COVID-19 patients. Journal of medical virology 2020.
25. Stoessl AJ, Bhatia KP, Merello M. Movement Disorders in the World of COVID-19. Movement disorders clinical practice 2020;7:355-6.
26. Sanchis-Gomar F, Lavie CJ, Perez-Quilis C, Henry BM, Lippi G. Angiotensin-Converting Enzyme 2 and Antihypertensives (Angiotensin Receptor Blockers and Angiotensin-Converting Enzyme Inhibitors) in Coronavirus Disease 2019. Mayo Clinic proceedings 2020.
27. Kuba K, Imai Y, Rao S, et al. A crucial role of angiotensin converting enzyme 2 (ACE2) in SARS coronavirus-induced lung injury. Nature medicine 2005;11:875-9.
28. Hoffmann M, Kleine-Weber H, Schroeder S, et al. SARS-CoV-2 Cell Entry Depends on ACE2 and TMPRSS2 and Is Blocked by a Clinically Proven Protease Inhibitor. Cell 2020;181:271-80 e8.
29. Sanders JM, Monogue ML, Jodlowski TZ, Cutrell JB. Pharmacologic Treatments for Coronavirus Disease 2019 (COVID-19): A Review. Jama 2020.
30. Sama IE, Ravera A, Santema BT, et al. Circulating plasma concentrations of angiotensin-converting enzyme 2 in men and women with heart failure and effects of renin-angiotensin-aldosterone inhibitors. European heart journal 2020;41:1810-7.
31. Li K, Wohlford-Lenane C, Perlman S, et al. Middle East Respiratory Syndrome Coronavirus Causes Multiple Organ Damage and Lethal Disease in Mice Transgenic for Human Dipeptidyl Peptidase 4. The Journal of infectious diseases 2016;213:712-22.
32. Netland J, Meyerholz DK, Moore S, Cassell M, Perlman S. Severe acute respiratory syndrome coronavirus infection causes neuronal death in the absence of encephalitis in mice transgenic for human ACE2. Journal of virology 2008;82:7264-75.
33. Papa SM, Brundin P, Fung VSC, et al. Impact of the COVID-19 Pandemic on Parkinson's Disease and Movement Disorders. Movement disorders clinical practice 2020;7:357-60.
34. Murray RS, Brown B, Brian D, Cabirac GF. Detection of corona-

virus RNA and antigen in multiple sclerosis brain. Annals of neurology 1992;31:525-33.
35. Finsterer J, Stollberger C. Causes of hypogeusia/hyposmia in SARS-CoV2 infected patients. Journal of medical virology 2020.
36. Chen Y, Liu Q, Guo D. Emerging coronaviruses: Genome structure, replication, and pathogenesis. Journal of medical virology 2020;92:418-23.
37. Wang D, Yin Y, Hu C, et al. Clinical course and outcome of 107 patients infected with the novel coronavirus, SARS-CoV-2, discharged from two hospitals in Wuhan, China. Crit Care 2020;24:188.
38. Liu K, Pan M, Xiao Z, Xu X. Neurological manifestations of the coronavirus (SARS-CoV-2) pandemic 2019-2020. Journal of neurology, neurosurgery, and psychiatry 2020;91:669-70.
39. Lai KN, Tsang KW, Seto WH, Ooi CG. Clinical, Laboratory, and Radiologic Manifestation of SARS. Current infectious disease reports 2004;6:213-9.
40. Wu Z, McGoogan JM. Characteristics of and Important Lessons From the Coronavirus Disease 2019 (COVID-19) Outbreak in China: Summary of a Report of 72314 Cases From the Chinese Center for Disease Control and Prevention. Jama 2020.
41. Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet 2020;395:1054-62.
42. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 2020;395:497-506.
43. Chen T, Dai Z, Mo P, et al. Clinical characteristics and outcomes of older patients with coronavirus disease 2019 (COVID-19) in Wuhan, China (2019): a single-centered, retrospective study. The journals of gerontology Series A, Biological sciences and medical sciences 2020.
44. Du Y, Tu L, Zhu P, et al. Clinical Features of 85 Fatal Cases of COVID-19 from Wuhan: A Retrospective Observational Study. American journal of respiratory and critical care medicine 2020.
45. Needham EJ, Chou SH, Coles AJ, Menon DK. Neurological Implications of COVID-19 Infections. Neurocritical care 2020.
46. Markus HS, Brainin M. COVID-19 and stroke-A global World Stroke Organization perspective. International journal of stroke : official journal of the International Stroke Society 2020:1747493020923472.
47. Ng Kee Kwong KC, Mehta PR, Shukla G, Mehta AR. COVID-19, SARS and MERS: A neurological perspective. Journal of clinical neuroscience : official journal of the Neurosurgical Society of Australasia 2020.
48. Matias-Guiu J, Gomez-Pinedo U, Montero-Escribano P, Gomez-Iglesias P, Porta-Etessam J, Matias-Guiu JA. Should we expect neurological symptoms in the SARS-CoV-2 epidemic? Neurologia 2020;35:170-5.
49. De Felice FG, Tovar-Moll F, Moll J, Munoz DP, Ferreira ST. Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) and the Central Nervous System. Trends in neurosciences 2020.
50. Tsai LK, Hsieh ST, Chang YC. Neurological manifestations in severe acute respiratory syndrome. Acta neurologica Taiwanica 2005;14:113-9.
51. Kim JE, Heo JH, Kim HO, et al. Neurological Complications during Treatment of Middle East Respiratory Syndrome. J Clin Neurol 2017;13:227-33.
52. Mao L, Jin H, Wang M, et al. Neurologic Manifestations of Hospitalized Patients With Coronavirus Disease 2019 in Wuhan, China. JAMA neurology 2020.
53. Herman C, Mayer K, Sarwal A. Scoping review of prevalence of neurologic comorbidities in patients hospitalized for COVID-19. Neurology 2020.
54. Lechien JR, Chiesa-Estomba CM, De Siati DR, et al. Olfactory and gustatory dysfunctions as a clinical presentation of mild-to-moderate forms of the coronavirus disease (COVID-19): a multicenter European study. Eur Arch Otorhinolaryngol 2020.
55. Baig AM. Neurological manifestations in COVID-19 caused by SARS-CoV-2. CNS neuroscience & therapeutics 2020;26:499-501.
56. Carod-Artal FJ. Neurological complications of coronavirus and COVID-19. Revista de neurologia 2020;70:311-22.
57. Lu L, Xiong W, Liu D, et al. New onset acute symptomatic seizure and risk factors in coronavirus disease 2019: A retrospective multicenter study. Epilepsia 2020.
58. Helms J, Kremer S, Merdji H, et al. Neurologic Features in Severe SARS-CoV-2 Infection. The New England journal of medicine 2020.
59. Oxley TJ, Mocco J, Majidi S, et al. Large-Vessel Stroke as a Presenting Feature of Covid-19 in the Young. The New England journal of medicine 2020;382:e60.
60. Beyrouti R, Adams ME, Benjamin L, et al. Characteristics of ischaemic stroke associated with COVID-19. Journal of neurology, neurosurgery, and psychiatry 2020.
61. Qureshi AI, Abd-Allah F, Alsenani F, et al. Management of acute ischemic stroke in patients with COVID-19 infection: Report of an international panel. International journal of stroke : official journal of the International Stroke Society 2020:1747493020923234.
62. Wang HY, Li XL, Yan ZR, Sun XP, Han J, Zhang BW. Potential neurological symptoms of COVID-19. Therapeutic advances in neurological disorders 2020;13:1756286420917830.
63. Tang N, Li D, Wang X, Sun Z. Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. Journal of thrombosis and haemostasis : JTH 2020;18:844-7.
64. Aggarwal G, Lippi G, Michael Henry B. Cerebrovascular disease is associated with an increased disease severity in patients with Coronavirus Disease 2019 (COVID-19): A pooled analysis of published literature. International journal of stroke : official journal of the International Stroke Society 2020:1747493020921664.
65. Kansagra AP, Goyal MS, Hamilton S, Albers GW. Collateral Effect of Covid-19 on Stroke Evaluation in the United States. The New England journal of medicine 2020.
66. Cui Y, Zhang ZF, Froines J, et al. Air pollution and case fatality of SARS in the People's Republic of China: an ecologic study. Environmental health : a global access science source 2003;2:15.
67. Martelletti L, Martelletti P. Air Pollution and the Novel Covid-19 Disease: a Putative Disease Risk Factor. SN comprehensive clinical medicine 2020:1-5.
68. Xu Z, Shi L, Wang Y, et al. Pathological findings of COVID-19

associated with acute respiratory distress syndrome. The Lancet Respiratory medicine 2020;8:420-2.
69. Chary MA, Barbuto AF, Izadmehr S, Hayes BD, Burns MM. COVID-19: Therapeutics and Their Toxicities. Journal of medical toxicology : official journal of the American College of Medical Toxicology 2020.
70. McKee DL, Sternberg A, Stange U, Laufer S, Naujokat C. Candidate drugs against SARS-CoV-2 and COVID-19. Pharmacological research 2020;157:104859.
71. de Abajo FJ, Rodriguez-Martin S, Lerma V, et al. Use of renin-angiotensin-aldosterone system inhibitors and risk of COVID-19 requiring admission to hospital: a case-population study. Lancet 2020.
72. Ferrario CM, Jessup J, Chappell MC, et al. Effect of angiotensin-converting enzyme inhibition and angiotensin II receptor blockers on cardiac angiotensin-converting enzyme 2. Circulation 2005;111:2605-10.
73. Mancia G, Rea F, Ludergnani M, Apolone G, Corrao G. Renin-Angiotensin-Aldosterone System Blockers and the Risk of Covid-19. The New England journal of medicine 2020.
74. Mackey K, King VJ, Gurley S, et al. Risks and Impact of Angiotensin-Converting Enzyme Inhibitors or Angiotensin-Receptor Blockers on SARS-CoV-2 Infection in Adults. Annals of internal medicine 2020.
75. Khera R, Clark C, Lu Y, et al. Association of Angiotensin-Converting Enzyme Inhibitors and Angiotensin Receptor Blockers with the Risk of Hospitalization and Death in Hypertensive Patients with Coronavirus Disease-19. medRxiv 2020051720104943 2020.
76. Mehra MR, Desai SS, Kuy S, Henry TD, Patel AN. Cardiovascular Disease, Drug Therapy, and Mortality in Covid-19. The New England journal of medicine 2020.