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The Covid-19 Pandemic: Manifestations and Complications of Neurological Disorders

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ABSTRACT

In late December 2019, an outbreak of a novel coronavirus causing severe acute respiratory syndrome (SARS) was reported in Wuhan, Hubei Province, China. The disease has been referred to as COVID-19, and the causative agent has been labelled SARS-CoV-2 due to its genetic resemblance to the virus SARS-CoV-1 responsible for SARS epidemic almost 20 years before. The epidemic has since spread to much of the world, having been considered as a pandemic with over 12 million confirmed cases and 5,52,143 deaths worldwide till July 10, 2020. COVID-19 pandemic demonstrates that infection with SARS-CoV-2 affects the central nervous system (CNS), the peripheral nervous system (PNS) and the muscle. Initially thought to be restricted to the respiratory system, it is now understood that COVID-19) also affects other multiple organs, including the central and peripheral nervous system. The number of recognized neurologic manifestations of SARS-CoV-2 infection is rapidly increasing. The pathobiology of the COVID-19 in CNS is still not known. Of the neurological disorders, some appear to be the consequence of direct viral invasion of the tissues of nervous systems, others arise as a postviral autoimmune process, and still, others are the result of metabolic and systemic complications due to the associated critical illness. This review deals with the preliminary observations regarding the neurological disorders reported with COVID-19 to date and illustrates some of the disorders that are anticipated from prior experience with similar coronaviruses.

Keywords: Clinical symptoms, Neurological diseases, Coronavirus, SARS-CoV-2, Stroke

INTRODUCTION

In December 2019, the first report of the Corona Virus Disease 2019 (COVID-19), an illness caused by the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was diagnosed from Wuhan, Hubei Province, China.

Symptoms of SARS-Cov-2 infection range from asymptomatic disease to life-threatening acute respiratory distress syndrome (ARDS), severe pneumonia, acute kidney injury, myocarditis, multi-organ failure and ultimately death. Most common symptoms of COVID-19 include fever, cough, fatigue, and shortness of breath. The epidemic has since spread to much of the world, having been considered as a pandemic with over 12 million confirmed cases in 188 countries and 5,52,143 deaths worldwide till July 10, 2020. India has confirmed more than 450,000 cases of COVID-19 so far, making it the world's fourth-worst-hit country. Metro cities like Kolkata, Delhi, Chennai, Ahmadabad and Mumbai are particularly badly affected, with hospitals struggling to accommodate critically ill patients. The coronavirus does not just target our lungs. A lot of research shows that COVID-19 is linked to potentially fatal brain damage and neurological problems. It is now understood that COVID-19 also affects other multiple organs, including the central and peripheral nervous system (Koralnik *et al*., 2020). The number of recognized neurologic manifestations of SARS-CoV-2 infection is rapidly increasing. According to a study published on July 8 in the journal Brain, some coronavirus patients experience brain swelling which is accompanied by episodes of delirium (Paterson *et al*., 2020). It has been proposed that the neuroinvasive potential of the novel SARS-CoV-2 may be at least partially responsible for the respiratory failure of patients with COVID-19 (Politi *et al*., 2020). Neurologists should therefore be apprised appropriately of COVID-19 infection for the benefit of the patient community as well as their own professional advantage. This review deals with the preliminary observations regarding the neurological disorders reported with COVID-19 to date.

The coronavirus: SARS-CoV-2

Structural characteristics and types

Coronaviruses, measuring 100–150 nm in diameter (McIntosh *et al*., 1985), are a family of enveloped, single-stranded, positive-strand RNA viruses classified within the order Nidovirales (Weiss *et al*., 2005). The nucleocapsid possesses a helical symmetry. By electron microscopy, coronaviruses display spike peptomer projections measuring 20 nm in length that are responsible for the virus' tropism. It is the 'crown-like' appearance of these projections that gave rise to the name coronavirus (Fehr *et al*., 2015). This coronavirus family consists of pathogens of many animal species and of humans, including the recently isolated severe acute respiratory syndrome coronavirus (SARS-CoV). Coronaviruses have been described for more than 50 years; for example, the isolation of the prototype murine coronavirus strain JHM, was reported in 1949 (Bailey et.al., 1949; Cheever et.al., 1949). The murine coronavirus mouse hepatitis virus (MHV) was studied as a model for human disease. This family of viruses remained relatively obscure, probably because there were no severe human diseases that could definitely be attributed to coronaviruses; human coronaviruses caused only the common cold. However, in the spring of 2003, when it became clear that a new human coronavirus was responsible for severe acute respiratory syndrome (SARS), coronaviruses became much more recognized. With the occurrence of the SARS epidemic, coronaviruses were then considered "emerging pathogens." (Weiss et.al., 2005).

Coronaviruses are classified into four genera: alpha (α), beta (β), gamma (γ), and delta (δ). Coronaviruses in the β genus include SARS, MERS, and the new coronavirus, referred to as SARS-Cov-2. There are now at least six human coronaviruses including SARS-CoV-1, SARS-CoV-2, MERS-CoV, HcoV-OC43, HCoV-229E, HCoV-NL-63, and HCoV-HKU1 (Arabi *et al*., 2015). SARS-CoV-2 was named for its close genetic relationship to the SARS virus. The "spike proteins" of both SARS (Imai *et al*., 2010) and SARS-CoV-2 (Lu *et al*., 2020) use the angiotensin-converting enzyme receptor type 2 (ACE-2) to bind to cells. The ACE-2 receptor is widely distributed in the body. It is widely present in the lungs, oral and nasal mucosa, bone marrow and spleen, skin, heart, arteries, kidneys, adipose tissue, reproductive system, and brain (Hamming *et al*., 2004).

General clinical manifestations of COVID-19

Coronaviruses in the animal kingdom have been associated with a variety of disorders, including infectious bronchitis, pneumonitis, nephrosis, gastroenteritis, encephalitis, enteritis, hepatitis and peritonitis (Berger 2020). The life threatening coronavirus infections identified in human have been respiratory infections, mainly mild upper respiratory infections. However, gastrointestinal disease has been observed in neonates and infants (McIntosh *et al*., 2005). It was also reported that coronaviruses cause acute and chronic respiratory, enteric, and central

nervous system (CNS) diseases in many species of animals, including humans (Weiss *et al*., 2005). Earlier to the emergence of SARS-CoV, there were two prototypes of human coronaviruses, OC43 and 229E, both etiologic agents of the common cold (McIntosh, 1974). There had long been speculation about the association of human coronaviruses with more serious human diseases such as multiple sclerosis (Burks et.al., 1980), hepatitis (Zuckerman et.al., 1970), or enteric disease in newborns (Resta et.al., 1985). However, none of these early associations had been substantiated. The recently identified SARS-CoV, which was shown to cause a severe acute respiratory syndrome was the first example of serious illness in humans caused by a coronavirus (Rota *et al*., 2003).

Neurological complications of COVID-19

Severe neurological complications of COVID-19 appear to be both infrequent and diverse in nature. Neurological disease may be the consequence of generalized cardiorespiratory failure and metabolic abnormalities triggered by the infection, direct invasion of the virus, or an autoimmune response to the virus (Berger, 2020). A latest review of neurological symptoms of COVID-19 patients reveals that the disease pretence a global threat to the entire nervous system. About half of hospitalized patients have neurological manifestations of COVID-19, which include headache, dizziness, decreased alertness, difficulty in concentrating, disorders of smell and taste, seizures, strokes, weakness and muscle pain (ScienceDaily, 2020).Virtually any part of the neuraxis appears to be at risk to injury with SARS-CoV-2 (Berger, 2020). According to Dr. Igor Koralnik, Northwestern Medicine chief of neuro-infectious diseases and global neurology and a professor of neurology at Northwestern University Feinberg School of Medicine, “It's important for the general public and physicians to be aware of this, because a SARS-COV-2 infection may present with neurologic symptoms initially, before any fever, cough or respiratory problems occur." (Koralnik *et al*., 2020).

Occurrence of Neurological Manifestation During SARS-COV-1

Several reports recently showed different neurological manifestations that could involve the central nervous system, the peripheral nervous system and musculoskeletal system (Guan *et al*., 2020; Huang *et al*., 2020; Mo *et al*., 2020; Wang *et al*., 2020a; Wang *et al*., 2020b). When SARS (caused by SARS-COV-1) first appeared in China in late 2002 and spreaded to other areas in Asia in early 2003 **(**Peiris *et al*., 2003), there were some limited reports of neurologic complications of SARS that appeared in patients 2 to 3 weeks into the course of the illness, mainly consisting of either an axonal peripheral neuropathy or a myopathy with elevated creatinine kinase (Tsai *et al*., 2004). Interestingly, there was a single report of a patient with SARS with olfactory neuropathy with onset of 3 weeks into the illness (Hwang, 2006). During the previous epidemic of SARS-CoV1, Umapathi *et al*. (2004) reported that, 5 among 206 patients with SARS in Singapore developed large-vessel strokes, 4 of these patients had their strokes in the setting of critical illness owing to SARS, and 3 were associated with significant episodes of hypotension.

Prevalence of Neurological Manifestation During SARS-COV-2 (Covid-19)

In view of the scarce history of neurologic manifestations of SARS-CoV-1–associated diseases, the recent report of Mao et. al., (2020) on detailed neurologic manifestations of the hospitalized patients with COVID19 from Wuhan is extremely important . They found among 214 hospitalized patient 78 (36.4%) had various neurologic manifestations that involved central nervous system (CNS), peripheral nervous system (PNS), and skeletal muscles (Mao *et al*., 2020). Another report on March 4, 2020, from Beijing Ditan Hospital found for the first time a case of viral encephalitis caused by a novel coronavirus (CoV) attacking the CNS. The researchers confirmed the presence of SARS-CoV-2 in the cerebrospinal fluid by genome sequencing and confirmed that COVID-19 has potential to cause nervous system damage (Xiang *et al*., (2020). Patients with severe infection were more likely to develop neurologic manifestations, especially acute cerebrovascular disease, conscious disturbance, and skeletal muscle injury. Most neurologic manifestations occurred early in the illness (within 1-2 days of hospital admission) (Mao *et al*., 2020**).** Broadly, some of the central nervous system manifestations, e.g. headache and dizziness and peripheral nervous system manifestations, e.g. hyposmia and hypogeusia occurred early, while encephalopathy with varying grades of altered sensorium and irritability occurred later, and in more severe illness, perhaps as a feature of multiorgan dysfunction. Some recent reports have emphasized hypospmia as a presenting manifestation of COVID-19 infection (Guan *et al*., 2020; Huang *et al*., 2020; Mo *et*

al., 2020; Wang *et al*., 2020a; Wang *et al*., 2020b). During the SARS epidemic in the year 2002–2003 several reports were there that revealed presence of different neurological disorders in COVID-19 (Berger, 2020). Earlier it was reported that after 3–4 weeks from the onset of coronavirus infection patients developed an axonal polyneuropathy (Tsai *et al*., 2005). Two patients developed myopathy and three rhabdomyolysis which were attributed to critical illness neuropathy and myopathy, though viral invasion could not be fully excluded (Tsai *et al*., 2005). Large vessel ischemic stroke was believed to be the consequence of multiple factors and patients with SARS in this period of epedemic were recognized as having a neurological complication (Tsai *et al*., 2005). In 2008, Netland (Netland et al ., 2008) and his group have demonstrated in a study in transgenic mice for ACE-2 receptor that SARS-CoV will enter the brain through the olfactory nerve and result in brain infection, but there is little cellular infiltration. Death in these infected transgenic mice has been attributed to respiratory failure from medullary infection (Netland *et al* ., 2008). Some investigators have suggested that a similar mechanism of respiratory distress may attend infection with SARS-CoV-2 (Li *et al*., 2020).

COVID-19 may affect the entire nervous system, including the brain, spinal cord and nerves as well as the muscles. There are many different ways by which COVID-19 can cause neurological dysfunction. Because this disease may affect multiple organs (lung, kidney, heart), the brain may also suffer from lack of oxygenation or from clotting disorders that may lead to ischemic or hemorrhagic strokes. In addition, the virus may cause direct infection of the brain and meninges. The reaction of the immune system to the infection may also cause inflammation that can damage the brain and nerves (ScienceDaily, 2020).

Direct effects of Covid-19 on Nervous System

The most common complaints for nervous system disorders due to COVIS-19 infection were dizziness, headache, hypogeusia, and hyposmia (Mao *et al*., 2020). It was also observed that neurologic symptoms were more common in patients with more severe disease (30.2% in nonsevere patients and 45.5% in severe patients) (Mao *et al*., 2020).

Headache is a common symptom of COVID-19 being observed in up to 40% of patients (Ding et. al., 2020). Typically, the headache has been regarded as mild. The frequency with which headache occurs due to a viral meningitis remains uncertain and will require further study. Similarly, the contribution of CNS viral invasion by SARS-CoV-2 contributes to the frequently observed altered levels of consciousness in the severely ill COVID-19 patient as opposed to general systemic disease. There is a least one report of the detection of SARS-CoV-2 from the cerebro spinal fluid (CSF) of a symptomatic man (Michael and Easton, 2020).

Myalgia or myositis is one of the common symptoms in COVID-19 infection. Muscle pain is a frequent manifestations reported in 35 to 50% of patients (Xu *et al*., 2020; Huang et al., 2020; Ding *et al*., 2020; Li et. al., 2020). Rhabdomyolysis may occur as a late complication and can result in life-threatening renal impairment. Careful monitoring of renal and muscle enzymes is thus important during SARS-CoV-2 infection (Jin and Tong, 2020).

According to a latest report by a leading American professional association of medical specialists, anosmia (loss of smell) and ageusia (loss of taste) may be the early symptom of Covid-19 infection. Currently, there have been reports of taste and smell disorders related to Covid-19 from multiple countries around the world. Loss of smell in association with upper respiratory infection is common and has been attributed to damage to olfactory epithelial by the causative virus (Seiden, 2004). Some investigators have proposed that the frequency with which upper respiratory tract infection (URI)-related olfactory loss is seen correlates with the type of virus responsible for the infection (Seiden, 2004). Anosmia has been reported in 30 to 66% and may be an early symptom of infection (Hopkins and Kumar, 2020). In mild infection, it may be the only clue of infection. Anosmia is often accompanied by ageusia (Guan *et al*., 2020; Zhou *et al*., 2020). Anosmia and ageusia related to COVID-19 typically resolve over several weeks (Berger, 2020).

Covid-19 and Stroke

Several pathophysiological processes may be responsible for an increased risk of stroke with COVID-19. As routine consultations and care are reduced or stopped, there is a possibility of worsening of neurological status due to lack of physical therapy and ongoing rehabilitation services. The unavailability of routine anticoagulation assay testing during the

epidemic might lead to increased risk of stroke, both haemorrhagic and occlusive due to inappropriate dosing without INR guidance. Severe disease is seen more often in older patients who often have co-morbidities that increase their risk of stroke. As with SARS (Tsai *et al*., 2005), a hypercoagulable syndrome may complicate COVID-19. Markers of coagulation may be increased during infection (Zhou *et al*., 2020), and circulated intravascular coagulation has been observed (Tang *et al.,* 2020). A viral myocarditis (Madjid *et al.*, 2020) may increase the risk of stroke. Lastly, brain endothelial express ACE-2 receptor and the potential exists for viral-induced vasculitis. Risk may be increased for both arterial and venous cerebrovascular disease. In one recent series of 78 COVID-19 patients, stroke occurred in 6 (2.8%) (5 ischemic and 1 hemorrhagic) (Mao *et al*., 2020). In a small series of 24 patients from the Seattle region, stroke was observed in 2 (8%) of 24 hospitalized COVID-19 patients (Bhatraju *et al*., 2020).

The more serious neurologic symptoms, such as stroke, ataxia, seizure, and depressed level of consciousness, all were more common in severely affected patients, accounting for the increased incidence in these patients (Mao *et al.,* 2020). However, these associations should be considered for understanding that patients with severe complications from SARS-COV-2 are more likely to have medical co-morbidities, especially vascular risk factors such as hypertension (Guan *et al*., 2020).

CONCLUSION

Coronavirus disease 2019 has now reached pandemic status and is widespread throughout the world. COVID-19 may infect nervous system and skeletal muscle as well as the respiratory tract. Patients with severe infection, neurologic involvement is greater, which includes acute cerebrovascular diseases, impaired consciousness, and skeletal muscle injury. Their clinical conditions may worsen, and patients may die sooner. Since knowledge about the long term outcome of neurologic manifestations of COVID-19 is limited, this review may offer important clinical information on COVID-19 that would help clinicians as well as neurologists to raise awareness of its involvement of neurologic manifestations. During this pandemic period of COVID-19, when considering patients with all these neurologic manifestations, clinicians should consider SARSCoV-2 infection as a differential diagnosis to avoid tardy diagnosis or misdiagnosis and prevention of transmission. No treatment has demonstrated high level evidence of proven efficacy till date, yet more than 200 clinical trials are underway around the world. Under such circumstances this glimpse into neurologic manifestations opens a porthole for the neurologists and places them on the front lines of the pandemic.

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Conflict of Interest

The author declares that there is no conflict of interest.

REFERENCES

Arabi Y M, Harthi A, Hussein J, Bouchama A, Johani S, et.al., (2015). Severe neurologic syndrome associated with middle east respiratory syndrome corona virus (MERS-CoV). *Infection,* 43(4): 495–501. doi: 10.1007/s15010-015-0720-y.

Bailey O T, Pappenheimer A M, Sargent F, Cheever M D,Daniels J B. (1949). A murine virus (JHM) causing disseminated encephalomyelitis with extensive destruction of myelin. II. Pathology. *Journal of Experimental Medicine,* 90: 195-212.

Berger J R. (2020). COVID-19 and the nervous system. *Journal of Neurovirology,*1–6.doi: 10.1007/s13365-020-00840-5

Bhatraju P K, Ghassemieh B J, Nichols M, Kim R, Jerome K R *et al*. ,(2020). Covid-19 in Critically Ill Patients in the Seattle Region — Case Series. *New England Journal of Medicine*, 382(21): 2012–2022. doi: 10.1056/NEJMoa2004500.

Burks J S, DeVald B L, Jankovsky L D, Gerdes J. (1980). Two coronaviruses isolated from central nervous system tissue of two multiple sclerosis patients. *Science,* 209: 933-934.

Cheever F S, Daniels J B, Pappenheimer A M, Bailey O T. (1949). A murine virus (JHM) causing disseminated encephalomyelitis with extensive destruction of myelin. I. Isolation and biological properties of the virus. *Journal of Experimental Medicine,* 90: 181-194.

Ding Q, Lu P, Fan Y, Xia Y, Liu M. (2020). The clinical characteristics of pneumonia patients co-infected with 2019 novel coronavirus and influenza virus in Wuhan, China. Journal of Medical Virology. doi: 10.1002/jmv.25781. Online ahead of print.

Fehr A R, Perlman S. (2015). Coronaviruses: an overview of their replication and pathogenesis. *Methods Molecular Biology.* 1282: 1–23. doi: 10.1007/978-1-4939-2438-7_1.

Guan W J, Ni Z Y, Hu Y, Liang W H, Ou C Q *et al*. (2020). Clinical characteristics of coronavirus disease 2019 in China. New England Journal of Medicine, 382: 1708-1720. doi: 10.1056/NEJMoa2002032

Hamming I, Timens W, Bulthuis M L, Lely A T, Navis G, *et al*. (2004). Tissue distribution of ACE2 protein, the functional receptor for SARS coronavirus. A first step in understanding SARS pathogenesis. *Journal of Pathology,* 203(2): 631–637. doi: 10.1002/path.1570.

Hopkins C, Kumar N. (2020). Loss of sense of smell as a marker of COVID-19 infection. ENTUK [cited 2020 March 30]; Available from: https://www.entuk.org/sites/default/files/files/Loss%20of%20sense%20of%20smell%20as%20marker%20of%20COVID.pdf

Huang C, Wang Y, Li X, Ren L, Zhao J *et al*. (2020). Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet*, 395(10223): 497–506. doi: 10.1016/S0140-6736(20)30183-5.

Huang C, Wang Y, Li X, Ren L, Zhao J, *et al*. (2020). Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet*, 395: 497–506.

Hwang C S. (2006). Olfactory neuropathy in severe acute respiratory syndrome: report of a case. *Acta Neurology Taiwan*. 15(1): 26-28.

Imai Y, Kuba K, Nakanishi T O., Penninger J M. (2010). Angiotensin-converting enzyme 2 (ACE2) in disease pathogenesis. *Circulation Journal,* 74(3): 405–410. doi: 10.1253/circj.CJ-10-0045.

Jin M, Tong Q. (2020). Rhabdomyolysis as Potential Late Complication Associated with COVID-19. *Emerging Infectious Diseases*, 26(7). doi: 10.3201/eid2607.200445 .

Koralnik I J, Tyler K L. (2020). COVID -19: a global threat to the nervous system. *Annals of Neurology*, 88(1): 1-11. doi: 10.1002/ana.25807.

Li L Q, Huang T, Wang Y Q, Wang Z P, Liang Y, *et al*., (2020). COVID-19 patients' patients' clinical characteristics, discharge rate, and fatality rate of meta-analysis. *Journal of Medical Virology*, 92(6): 577-583.doi: 10.1002/jmv.25757.

Li Y C, Bai W Z., Hashikawa T. (2020a) The neuroinvasive potential of SARS-CoV2 may play a role in the respiratory failure of COVID-19 patients. *Journal of Medical Virology,* 92(6): 552-555. doi: 10.1002/jmv.25728. https://www.ncbi.nlm.nih.gov/pubmed/32104915

Lu R, Zhao X, Li J, Niu P, Yang B et.al., (2020). Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding. *Lancet*, 395(10224): 565–574. doi: 10.1016/S0140-6736(20)30251-8.

Madjid M, Naeini P S, Solomon S D, Vardeny O *et al*., (2020). Potential effects of coronaviruses on the cardiovascular system: a review. *JAMA Cardiology*, E1-E10. Archived from: https://jamanetwork.com/

Mao L, Wang M, Chen S, He Q, Chang J, *et al*. (2020). Neurologic Manifestations of Hospitalized Patients With Coronavirus Disease 2019 in Wuhan, China. *JAMA Neurol*ogy, 77(6): 683-690. doi:10.1001/jamaneurol. 2020. 1127.

McIntosh K *et al*., (1985). Coronaviruses. In: Fields BN, *et al*., editors. Field's Virology. New York: Raven Press, pp.1323–1330.

McIntosh K, Anderson L J. (2005). Coronaviruses, including severe acute respiratory distress syndrome (SARS)-associated coronavirus. In: Mandell GL, Bennett JE, Dolin R, editors. Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases. Philadelphia: Elsevier Churchill Livingston, pp.1990–1997.

McIntosh K. (1974). Coronaviruses: a comparative review. *Current Topics in Microbiology and Immunology,* 63: 85-129.

Michael B, Easton A. (2020). COVID-19 and encephalitis. [cited 2020 March 30]; Available from: www.encephalitis.info/blog/coronavirus

Mo P, Xing Y, Xiao Y, Deng L, Zhao Q, *et al*. (2020). Clinical characteristics of refractory COVID-19 pneumonia in Wuhan, China. *Clinical Infectious Disease*. doi:10.1093/cid/ciaa270.

Netland J, Meyerholz D K, Moore S, Cassell M, Perlman S. (2008). Severe acute respiratory syndrome coronavirus infection causes neuronal death in the absence of encephalitis in mice transgenic for human ACE2. *Journal of Virology,* 82(15): 7264–7275. doi: 10.1128/JVI.00737-08.

Northwestern University. "COVID-19 threatens the entire nervous system: Neurological symptoms may appear before fever or cough." ScienceDaily, 11 June 2020. <www.sciencedaily.com/releases/2020/06/200611152444.htm>.

Paterson R W, Brown R L, Benjamin L, Nortley R, Wiethoff S, *et al*. The emerging spectrum of COVID-19 neurology: clinical, radiological and laboratory findings. *Brain*, awaa240, https://doi.org/10.1093/brain/awaa240 08 July 2020.

Peiris J S M, Yuen K Y, Osterhaus A D M E, Stöhr K. (2003). The severe acute respiratory syndrome. *New England Journal of Medicine*, 349(25): 243.

Politi L S, Salsano E, Grimaldi, M. (2019). Magnetic Resonance Imaging Alteration of the Brain in a Patient With Coronavirus Disease 2019 (COVID-19) and Anosmia. *JAMA Neurology,* Published online May 29, 2020. https://jamanetwork.com/

Resta S, Luby J P, Rosenfiled CR, Siegel J D. (1985). Isolation and propagation of a human enteric coronavirus. *Science*, 229: 978-981.

Rota P A, Oberste M S, Monroe S S, Nix W A, Campagnoli R, *et.al.* (2003). Characterization of a novel coronavirus associated with severe acute respiratory syndrome. *Science*, 300: 1394-1399.

Seiden A M. (2004). Postviral olfactory loss. *Otolaryngologic Clinics of North America.* 37(6): 1159–1166. doi: 10.1016/j.otc.2004.06.007.

Tang X, Wu C, Li X, Song Y, Yao X *et al*. (2020). On the origin and continuing evolution of SARS-CoV-2. *National Science Review*, 7(6): 1012-1023. doi: 10.1093/nsr/nwaa036.

Tsai L K, Hsieh S T, Chao C C, *et al*. (2004). Neuromuscular disorders in severe acute respiratory syndrome. *Archive of Neurology*, 61(11): 1669-1673. doi:10.1001/archneur.61.11.1669.

Tsai L K, Hsieh S T, Chang Y C. (2005). Neurological manifestations in severe acute respiratory syndrome. *Acta Neurol Taiwanica,* 14(3): 113–119.

Umapathi T, Kor A C, Venketasubramanian N, *et al*. (2004). Large artery ischaemic stroke in severe acute respiratory syndrome (SARS). *Journal of Neurolgy,* 251 (10): 1227-1231. doi:10.1007/s00415-004-0519-8.

Wang D, Hu B, Hu C, Zhu F, Liu X, *et al*. (2020a). Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus-Infected Pneumonia in Wuhan, China. JAMA. doi:10.1001/jama 2020.1585.

Wang Z, Yang B, Li Q, Wen L, Zhang R. (2020b). Clinical features of 69 cases with coronavirus disease 2019 in Wuhan, China. *Clinical Infectious Disease,* doi:10.1093/cid/ciaa272.

Weiss S R, Martin S N. (2005). Coronavirus Pathogenesis and the Emerging Pathogen Severe Acute Respiratory Syndrome Coronavirus. *Microbiology Molecular Biology Review*. 69(4): 635–664.

Xiang, P, Xu X M, Gao L L, Wang H Z, Xiong H F, *et al*., (2020). First case of 2019 novel coronavirus disease with Encephalitis. *China Xiv*. 2020;T202003:00015.

Xu X W, Xiao X W, Xian G J, Kai J X, Ling J Y. *et al*. (2020). Clinical findings in a group of patients infected with the 2019 novel coronavirus (SARS-Cov-2) outside of Wuhan, China: retrospective case series. *British Medical Journal*, 368:m606. doi: 10.1136/bmj.m606.

Zhou F, Yu T, Du R, Fan G, Liu Y *et al*. (2020) Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet*, 395(10229): 1054-1062.

Zuckerman A J, Taylor P E, Almeida D. (1970). Presence of particles other than the Australia-SH antigen in a case of active hepatitis with cirrhosis. *British Medical Journal,* 1: 262-264.