



Neurological injuries in COVID-19 patients: direct viral invasion or a *bystander* injury after infection of epithelial/endothelial cells

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Received: 29 June 2020 / Revised: 11 August 2020 / Accepted: 24 August 2020 / Published online: 2 September 2020
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Abstract

A subset of patients with *coronavirus 2* disease (COVID-19) experience neurological complications. These complications include loss of sense of taste and smell, stroke, delirium, and neuromuscular signs and symptoms. The etiological agent of COVID-19 is *SARS-CoV-2* (severe acute respiratory syndrome coronavirus 2), an RNA virus with a glycoprotein-studded viral envelope that uses ACE2 (angiotensin-converting enzyme 2) as a functional receptor for infecting the host cells. Thus, the interaction of the envelope spike proteins with ACE2 on host cells determines the tropism and virulence of *SARS-CoV-2*. Loss of sense of taste and smell is an initial symptom of COVID-19 because the virus enters the nasal and oral cavities first and the epithelial cells are the receptors for these senses. Stroke in COVID-19 patients is likely a consequence of coagulopathy and injury to cerebral vascular endothelial cells that cause thrombo-embolism and stroke. Delirium and encephalopathy in acute and post COVID-19 patients are likely multifactorial and secondary to hypoxia, metabolic abnormalities, and immunological abnormalities. Thus far, there is no clear evidence that coronaviruses cause inflammatory neuromuscular diseases via direct invasion of peripheral nerves or muscles or via molecular mimicry. It appears that most of neurologic complications in COVID-19 patients are indirect and as a result of a *bystander* injury to neurons.

Keywords COVID-19 · Stroke · ACE2 · Taste · Smell · Encephalopathy · Tropism · SARS-CoV-2

In 2019, a new coronavirus disease (COVID-19) emerged, sparking a worldwide pandemic that has led to significant morbidity and mortality and stressed the health systems globally. Since the beginning of the pandemic, a deluge of unfiltered information has streamed into the scientific journals and mainstream media about COVID-19 and its etiological agent, *SARS-CoV-2*. This “infodemic” has often been in equal parts valuable, redundant, confusing, and contradictory. Although *SARS-CoV-2* initially injures the respiratory tract, it also affects other organs including the nervous system (Helms et al. 2020a, b; Guan et al. 2020; Mao et al. 2020). Here, we review the salient features of *SARS-CoV-2* pathogenesis and highlight the mechanisms of neurologic complications of the *SARS-CoV-2* infection.

Human coronavirus 2 (*SARS-CoV-2*)

The family of *coronaviruses* are a successful group of microbial pathogens that depend on the living cells for replication and infect many species of birds and mammals (Poutanen 2018). During the millions of years of coexistence, a complex system of cohabitation has evolved between viruses and their host cells. At different stages of this evolution, flare-ups of destructive infection in the host population can occur that eventually reach a homeostasis. COVID-19 can be considered such a destructive infection phase. *SARS-CoV-2* is an RNA virus that belongs to the *beta coronavirus* genus and similar to *SARS-CoV-1* and the Middle Eastern respiratory syndrome (MERS) is host- and cell-specific (Lu et al. 2020; Luis et al. 2015). The virus is a zoonotic pathogen native to bats and is likely transmitted to humans via an as yet unknown intermediary (Lu et al. 2020; Luis et al. 2013). Bats and rodents are rich sources of zoonotic viruses because different species of these animals share the same viruses allowing the virus to adapt to different hosts (Luis et al. 2013). Once the *coronavirus* achieved a hold in the human host, it has made further adaptations. New clades of virus have accelerated

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human-to-human transmission, contributing to the severity of the pandemic (Li et al. 2020; Korber et al. 2020; Andersen et al. 2020). *SARS-CoV-2* is primarily transmitted from human to human by inhalation of virus containing airborne droplets in crowded closed quarters and also via a possible fecal to oral route (Lamers et al. 2020; Xu et al. 2020a). Although *SARS-CoV-2* carries “respiratory” in its moniker, it exploits the broadly expressed angiotensin-converting enzyme 2 (ACE2) for entry into the target endothelial and epithelial cells (Li et al. 2003; Shang et al. 2020a, b). This contributes to both the specificity and breadth of infection, as other organs and organ systems that contain epithelial cells, including the nervous system, are affected (Guan et al. 2020; Mao et al. 2020).

SARS-CoV-2 is a large positive-sense, single-stranded, non-segmented RNA that is enclosed in a nuclear capsid. The RNA genome is over 29,000 bases. Another noteworthy feature of *coronaviruses* in general, *SARS-CoV-2* included, is their glycoprotein-studded viral envelope. The lipid envelope, a remnant of the previous host cell membrane, dictates viral stability and its infectivity. The proteins imbedded in this envelope mediate viral entry into the host cells (Figs. 1 and 2) and are important in allowing the virus to evade host immune surveillance (Zhang et al. 2020a, b, c; Shang et al. 2020b; Alcami and Koszinowski 2000). Each of the spike proteins in the viral ectodomain is comprised of a trimer of glycoproteins (S1, Figs. 1 and 2) that are mounted on a stalk (S2) like an ice cream cone (Fig. 1b) (Walls et al. 2020; Wrapp et al. 2020; Shang et al. 2020a, b). Spike proteins are translated from the viral RNA and determine the virulence and tropism of the virus (Lu et al. 2020; Luis et al. 2015). Therefore, attention has quickly focused on the structure and function

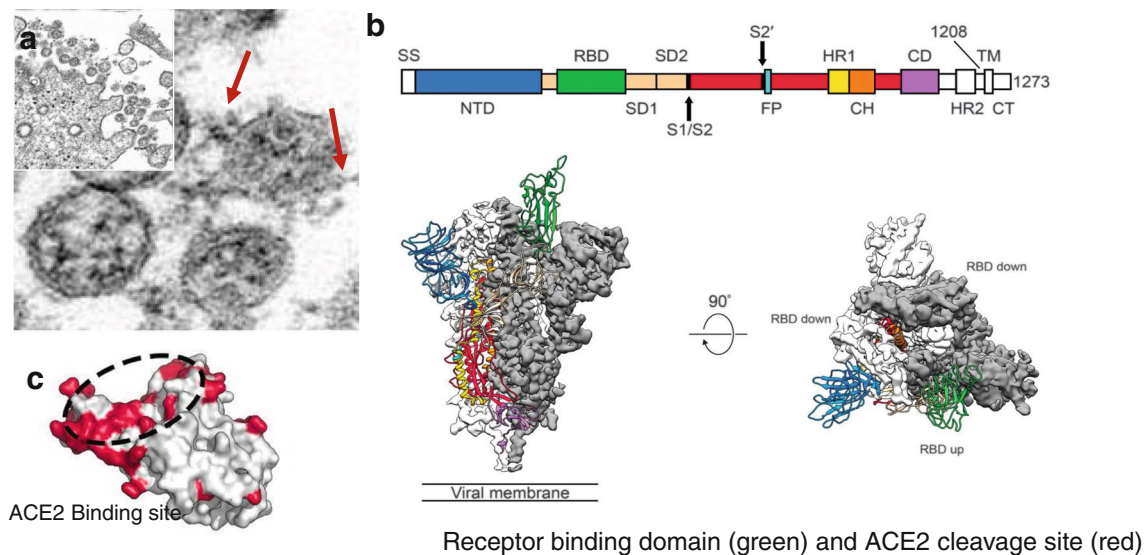


Fig. 1 Images of *SARS-CoV-2* and its spike protein. **a** Electron microscope images of crown-shaped *SARS-CoV-2* with protein spikes (red arrows). **b** Structure of protein spikes showing the receptor-binding domain (green) that attaches to ACE2 and the site of enzymatic cleavage

Viral attachment and entry into host cells

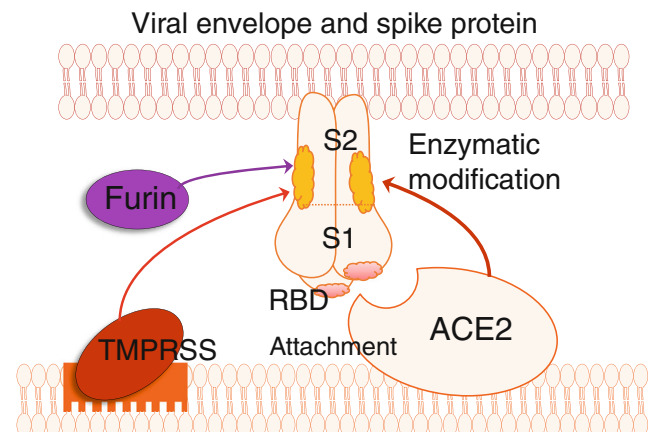


Fig. 2 Diagram depicting a compilation of data on attachment and fusion of coronavirus with the host cell. *Attachment* occurs by fastening of the receptor binding domain (RBD, Fig. 1c) to the ACE2 as a functional receptor. RBD is a variable segment and a target of treatment (see text). The spike proteins undergo conformational changes to fuse virus and cell membranes in order to allow delivery of the viral genome into the target cells. The structural rearrangements are accomplished by enzyme assisted proteolysis involving the *transmembrane serine protease 2* (TMPRSS2), *Furin*, and *ACE2*. The substrate for these proteolytic enzymes is the polybasic cleavage site (yellow) at the S1-S2 junction of the spike protein. ACE2 plays an indispensable role as it provides a docking port for *SARS-CoV2* and facilitates fusion via enzymatic modification of the spike proteins

of the *SARS-CoV-2* spike proteins as therapeutic targets and for vaccine development (Lan et al. 2020; Shang et al. 2020a, b; Corbett et al. 2020; Ju et al. 2020).

(yellow) that allow conformational changes in the spike protein to facilitate fusing of viral envelope with host cell membrane. **c** Another view of spike protein with sticky binding sites (red). (From Wrapp et al. 2020, with permission)

Infection of host cells by SARS-CoV-2

Identifying the steps involved in the mode of infection of host cells by *SARS-CoV-2* will help us understand the phenotype of neurological disease in COVID-19. *SARS-CoV-2* spike proteins mediate viral entry into the host cells through a complex molecular dance with the target host cells. This interaction occurs in two steps, *attachment* of viral envelope glycoproteins (S1) to ACE2, and *fusion* of viral envelope to the host cell membrane (Tortorici and Veesler 2019; Lan et al. 2020; Walls et al. 2016, 2020). *Attachment* occurs when the receptor-binding domain (RBD) of spike protein fastens to ACE2 (Figs. 1, 2). RBD is a variable domain located on the outer side of the spike protein (Fig. 1c) and has been the target for treatment of COVID-19 by neutralizing antibodies (Ju et al. 2020; Shi et al. 2020; Wrapp et al. 2020; Walls et al. 2020; Shang et al. 2020b). ACE2 is a cognate cell surface receptor for *SARS-CoV-2* and determines its tropism. The next step in target cell infection is *fusion* of the coronavirus envelope with the host cell membrane that is driven by changes in the conformation of the viral spike proteins (Belouzard et al. 2012; Heald-Sargent and Gallagher 2012). The conformational changes are accomplished by the host enzymes including transmembrane serine protease 2 (*TMPRSS2*); Furin and ACE2 are epithelial specific proteolytic enzymes (Stopsack et al. 2020; Braun and Sauter 2019; Walls et al. 2020; Shang et al. 2020a). They cleave a polybasic site at the S1-S2 junction of the spike protein (Fig. 2) and rearrange its structure (Belouzard et al. 2012; Heald-Sargent and Gallagher 2012) allowing the viral envelope to fuse with the target cell membrane.

Since cells that harbor ACE2 are the main targets of *SARS-CoV-2* infection, ACE2 determines viral tropism and by extension disease phenotype and virulence. Thus, it is important to appreciate its localization in the body. Studies of the protein distribution demonstrate that *ACE2* is concentrated primarily on the surface of endothelial cells and the epithelium of the exposed mucosa, such as the linings of the nasal and oral cavities, the lungs, and the gut (Ackermann et al. 2020; Hamming et al. 2004; Sungnak et al. 2020; Xu et al. 2020a, b). Since lungs are mostly comprised of epithelial and endothelial cells and are exposed to the aerosol transmission, they become infected early and severely. Also, the initial clinical manifestation of *SARS-CoV-2* infections has been reported in conjunctiva (Chen et al. 2020), nasal cavity lining (Sungnak et al. 2020), oral cavity lining (Xu et al. 2020a, b), and gastrointestinal lining (Zhang et al. 2020a, b, c). All these areas are lined with epithelial cells that harbor ACE2 on their surface accounting for early clinical findings in COVID-19.

While ACE2 serendipitously facilitates *coronavirus* entry into the host cells (Li et al. 2003; Shang et al. 2020a, b), it also has significant physiological roles in homeostatic regulation of blood circulation as a vasoprotective and cardioprotective

agent (Kuba et al. 2013). ACE2 serves as a counterbalance to ACE (angiotensin-converting enzyme and deactivates angiotensin II) by reducing the blood pressure (Kuba et al. 2013). In the gut mucosa, ACE2 regulates the intestinal amino acid transporters (Zhang et al. 2020a, b, c). There has been much speculation as to whether a commonly used class of antihypertensive drugs, the ACE inhibitors, has any influence on COVID-19. The available data (Reynolds et al. 2020; Mancina et al. 2020) indicate that these drugs have no effect on prevalence or infectivity of *SARS-CoV-2*. Once the viral RNA enters the target cells by endocytosis, it starts to translate and efficiently replicate (Sawicki 2009) and injure the host cells. Enveloped viruses such as *SARS-CoV-2* generally form a cytopathic infection in the host cells and these cells can become viral reservoirs. Each of these steps represent a possible target for therapeutic intervention in COVID-19 (Corbett et al. 2020).

Neurological manifestations of COVID-19

The above discussion lays the ground work for understanding neuropsychiatric manifestations COVID-19. While a number of viruses infect the non-neural cells in the nervous system, only a few viruses such as herpes (Kleinschmidt-DeMasters and Gildea 2006) and rabies (Wang et al. 2018; Lafon 2008) directly infect neurons via specific receptors. This is because evolutionarily most pathogenic viruses require a complex chemical dance with the target cells before entering the cell, as discussed above. The phenotypes of the virally mediated neurological diseases depend on the type of infected cells and the affected neural networks. For example, human immunodeficiency virus (HIV) establishes a cytopathic infection in microglia and astrocytes (Castellano et al. 2017) and these cells can serve as reservoirs of viral particles (Ghafouri et al. 2006) and indirectly affecting neurons. Common systemic viral infections, including *SARS-CoV-2*, are known to indirectly involve the nervous system triggering acute and or chronic neuropsychiatric syndromes (Helms et al. 2020a; Mao et al. 2020; De Felice et al. 2020). The nervous system is vulnerable to immune dysregulations because of its special immune status (Billingham et al. 1953); thus, an immune reaction that is triggered by a systemic viral infection can injure the nervous system (Ghafouri et al. 2006). A number of nervous system injuries have been associated with COVID-19 including stroke (Yaghi et al. 2020; Oxley et al. 2020), loss of sense of taste and smell (Menni et al. 2020; Cooper et al. 2020), Guillain-Barre syndrome (Toscano et al. 2020), and upper motor neuron signs with abnormal MRI and EEGs (Helms et al. 2020a, b) as well as neuropsychiatric disorders (Helms et al. 2020a, b; Rogers et al. 2020). The mechanisms of neurological manifestations of COVID-19 and the

sequence of pathogenesis of these conditions are not fully understood yet.

Stroke

Recent reports (Yaghi et al. 2020; Oxley et al. 2020) associated COVID-19 with large vessel strokes in a group of relatively young patients without significant stroke risk factors. Also, many patients with stroke have tested positive for *SARS-CoV-2* and vice versa (see Table 1). These studies suggest a potential increased risk for stroke and stroke as a contributor of increased morbidity and mortality in patients with COVID-19 (Yaghi et al. 2020; Qin et al. 2020; Mao et al. 2020). However, the total number of patients admitted to the hospitals including ours for evaluation of acute stroke during COVID-19 crisis declined (Kansagra et al. 2020). This is similar to the rate of admissions for evaluation of acute myocardial infarction (Solomon et al. 2020a). The decline in hospitalizations during the peak of outbreak was likely due to the fear of COVID-19, where patients with signs and symptoms of stroke avoid or postpone seeking help and also aggressive triage by the ED personnel to avoid unnecessary hospital admissions because of paucity of hospital beds. The question that remains unanswered is whether COVID-19 is an independent or a contributory risk factor for stroke? If so, what is the mechanism of stroke in COVID-19 patients? Stroke is an acute and focal loss of neurological function brought on by an abrupt cessation of blood supply to a portion of the brain. Pathogenesis of stroke involves the heart, large and small blood vessels, and blood itself, harking back to the Virchow's triad of thrombosis: irritation of vessels, blood coagulation, and interruption of blood flow (Bagot and Arya 2008). It appears that in COVID-19 patients the proximate causes of stroke are coagulopathy and injury to cerebral vascular endothelial cells (Fig. 3).

Table 1 A listing of studies on stroke in COVID-19 patients. In general, reports demonstrate coagulopathy and the ensuing complications including stroke. Case reports are not included

Studies	No. of COVID-19 patients	No. of strokes	Age
*Oxley et al.	–	5	33–49
Helms et al.	150	7 (4.7%)	63
Klok et al.	184	5 (2.7%)	64
Mao et al.	214	6 (2.8%)	52.7
*Qin et al.	1875	50 (2.7%)	63
Yaghi et al.	3556	32 (0.9%)	40s–70s
Lodigiani et al.	362	9 (2.5%)	66
Merkler et al.	1916	31 (1.6%)	69

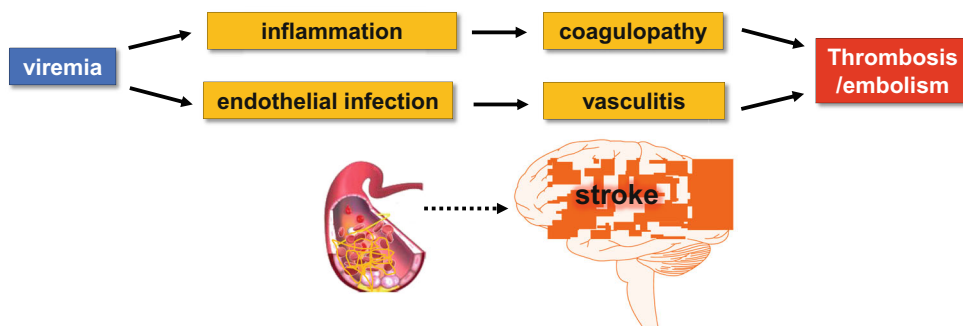
*These reports explore effects of stroke on COVID-19 and vice versa

Once the nosocomial infection with *SARS-CoV-2* is established, spilling of viral particles into the blood stream causes viremia that can then infect cerebral blood vessels. The endothelial lining of the cerebral blood vessels is rich in ACE2 (discussed above; Fig. 4 in Hamming et al. 2004), which makes them targets for *SARS-CoV-2* infection. Viral infection and proliferation of viral particles in the vascular endothelial cells injure the lining of blood vessels causing endothelialitis (Pugin et al. 2020; Varga et al. 2020). The injury can initiate thrombosis leading to strokes (Fig. 3). Also, a significant *SARS-CoV-2* viremia can disrupt function of ACE2 in the cerebral vessels and interrupt its vasoprotective function (Kuba et al. 2013). Local immune response can be another cause of injury to the cerebral vessels. Viral antigens can activate the complement system, macrophages, and neutrophils that then damage the endothelial cells. The complement system forms the membrane attack complex (MAC) that if left unregulated, MAC injures endothelial cells (Magro et al. 2020; Song and Fitzgerald 2020). Even a small injury to the lining of the cerebral vessels can initiate in situ thrombosis (Dubois et al. 2007; Atkinson et al. 2010) and subsequently large or small strokes (Fig. 3).

The second major reason for stroke is coagulopathy, which is associated with COVID-19 (Klok et al. 2020a, b; Helms et al. 2020b). Autopsy of COVID-19 decedents and the pathological analysis revealed that both veins and arteries in multiple areas of body contained blood clots (Varga et al. 2020). Another study revealed that 31% of patients admitted to ICUs with COVID-19 showed complications of thrombosis such as pulmonary embolism and deep venous thrombosis and stroke (Klok et al. 2020a, b). The high rate of coagulopathy is attributed to a robust immune response triggered by *SARS-CoV-2* infection. Humoral immune response is known to contribute to thrombosis by forming antibodies such as anti-phospholipid antibodies. In patients with systemic lupus erythematosus, anti-phospholipid antibodies in circulation are used as clinical markers of thrombosis and stroke (Janardhan et al. 2004; Kitagawa 2005). Increased levels of anti-phospholipid antibodies have been reported in COVID-19 patients with coagulopathy (Zhang et al. 2020c). It is also known that shortly after the onset of COVID-19, an antibody response to *SARS-CoV-2* develops (Ni et al. 2020; Haveri et al. 2020; Shi et al. 2020). Some of the antibodies are neutralizing antibodies against the virus and preliminary clinical observations suggest that they may mitigate *SARS-CoV-2* infection (Kreer et al. 2020; Shi et al. 2020; Bloch et al. 2020). However, this protective antibody reaction is not a likely risk factor for stroke (Joyner et al. 2020).

In addition to antibody response, another reason for the coagulopathy is cytokine and metabolic dysregulation triggered by *SARS-CoV-2* (Shen et al. 2020). Activation of neutrophils by the complement system promotes formation of neutrophil external traps (NETs) that can trigger clot

Fig. 3 A box-and-arrow diagram depicting the pathogenesis of stroke in COVID-19 patients. The two proximate causes of stroke are cerebral vascular endothelialitis and coagulopathy; these can result in embolic and thrombotic strokes

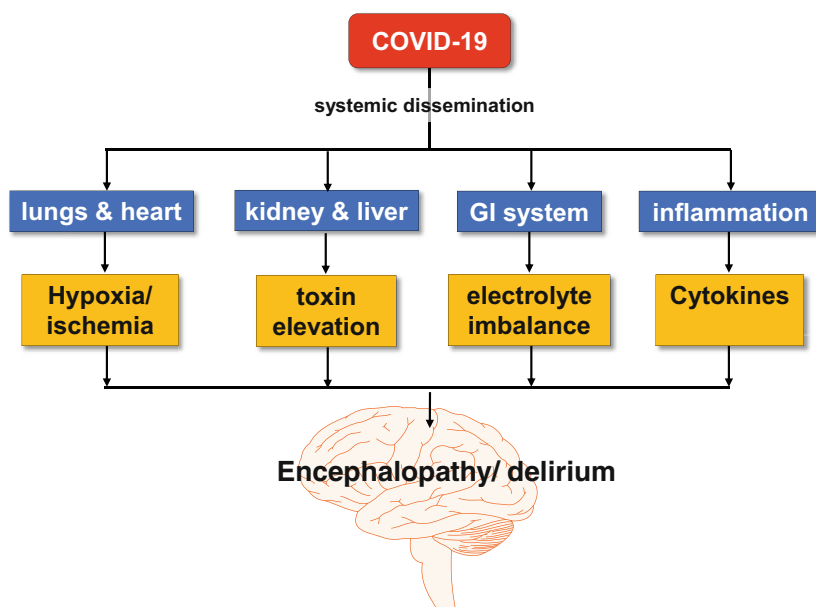


formation (Barnes et al. 2020; Becker 2020). Release of cytokines, particularly IL-6, activate cell-mediated immune response against the viral antigens. However, reports of basic laboratory values and our own observations indicate only mild to moderate leukocytosis and minimal elevation of neutrophils in majority of COVID-19 patients (Zhang et al. 2020a, b, c; Huang et al. 2020). On the other hand, spilling of viral particles, antigenic proteins, and debris from injured infected cells can represent risk factors for thrombosis. For example, it is known that free RNA, released after cell injury into blood stream, can initiate thrombosis (Kannemeier et al. 2007). In patients with COVID-19, viral proteins and RNA as well as cellular debris after cytolytic destruction of endothelial cells can present a significant risk for coagulopathy and stroke. Neuroimaging studies of COVID-19 patients with neurological symptoms reveal that hypoxia and stroke are the most common findings in these patients (Jain et al. 2020). In summary, SARS-CoV-2 infection can contribute to stroke by initially causing vasculitis and coagulopathy that can lead to both thrombotic and embolic strokes (Fig. 3).

Loss of sense of taste and smell

Loss of sense of taste and smell has been reported as the initial clinical manifestations of COVID-19. They are the most common self-reported initial symptoms among patients who tested positive for SARS-CoV-2 infection (Menni et al. 2020; Cooper et al. 2020). The clinical validity of these symptoms is clear and follows our discussion about the mode of contagion and tropism of the SARS-CoV-2 infection. SARS-CoV-2 containing airborne droplets first come in contact with the ACE2-rich epithelium of the nasal and oral mucosa (Sungnak et al. 2020; Xu et al. 2020a, b) infecting these cells. Since epithelial cells are the chemical receptors for the sense of taste and smell, injury to these cells result in alteration of sense of taste and smell. Transient olfactory bulb edema in a COVID-19 anosmic patient has been reported; this indicates involvement of neurovascular complex (Laurendon et al. 2020). Though a neuropathological study and RT-PCR of human olfactory bulb tissues infected with SARS-CoV2 did not reveal SARS-CoV-2 infection or injury to the neural tissues (Solomon et al.

Fig. 4 A box-and-arrow diagram showing the clinical genesis and multifactoriality of encephalopathy and delirium in COVID-19 patients



2020b). Thus, loss of senses of taste and smell is likely due to epithelial injury and can be an initial clinical indicator of *SARS-CoV-2* infection, and can point to a population that should be tested for *SARS-CoV-2* (Menni et al. 2020) and triaged as such.

COVID-19 and neuromuscular system

A subset of patients with COVID-19 present with neuromuscular disorders including weakness, sensory loss, and acute neuropathy or Guillain-Barre syndrome (Alberti et al. 2020; Sedaghat and Karimi 2020; Toscano et al. 2020). It is conceivable that the observed neuropathy in COVID-19 patients is inflammatory through delayed immune response and molecular mimicry. This is similar to other viral and bacterial infections that are associated with Guillain-Barre syndrome including *Campylobacter jejuni* (Godschalk et al. 2004; Nachamkin et al. 1998), HIV (Goldstein et al. 1993; Shepherd et al. 2017), cytomegalovirus (Visser et al. 1996) and Zika virus (de Siqueira et al. 2016), where an immune response that is directed against an antigenic epitope of the pathogen also attacks a similar glycoprotein on the surface of myelin and or axon, causing immune-mediated injury. However, it is curious that there are only a few reported cases of inflammatory motor neuropathy associated with other similar *coronaviruses* such as *SARS-CoV-1* and *MERS* virus (Kim et al. 2017).

A portion of neuromuscular disorders reported in gravely ill COVID-19 patients with prolonged convalescence could be due to critical illness neuropathy and myopathy (Latronico et al. 1996). As further reports of neuromuscular abnormalities are revealed, we will be able to determine the specific incidence and mechanism of these conditions in COVID-19 patients.

COVID-19 and neuropsychiatric issues

Neuropsychiatric issues including impaired consciousness, lethargy, disorientation, and headache have been reported in a group of COVID-19 patients (Kotfis et al. 2020; Rogers et al. 2020). In the acute phase of COVID-19 illness, critically ill patients exhibit encephalopathy in a range of intensities, from almost no effect to severe delirium. The intensity of condition is related to duration and severity of illness. During the acute and convalescent stages of COVID-19, vulnerable patients manifest impaired consciousness, disorientation, and altered mentation (Kotfis et al. 2020; Helms et al. 2020a, b; Larvie et al. 2020). Clinically, these effects are manifested as delirium and later as cognitive deficits (Helms et al. 2020a, b; Rogers et al. 2020; Fong et al. 2011). Delirium is an acute disruption of information processing by the brain

sensory networks and the ensuing aberrant behavior. It is clinically manifested as alteration in both perceptual and behavioral domains and is often observed as agitation in the patients confined to the intensive care units. Delirium is caused by hypoxia, metabolic derangements, and inflammation; thus, it can be fluctuating and reversible (Fig. 4). The term encephalitis has been loosely used to refer to neurologic manifestations of systemic viral infections, though neurons are highly differentiated cells and remain resistant to viral entry and infection. No specific neuropsychiatric illness has been attributed to *SARS-CoV-2* and as yet there is no evidence that *SARS-CoV-2* infects neurons directly. It has been speculated that *SARS-CoV-2* can spread to the temporal lobes via the olfactory tract infection, causing encephalopathy. However, a recent neuropathology study from an autopsy series of COVID-19 decedents demonstrate mainly hypoxic injury to the brain (Solomon et al. 2020b). A survey of COVID-19 hospitalized patients with neuropsychiatric symptoms did not reveal infected CSF (Helms et al. 2020a). On the other hand, the cerebral vessels are in direct contact with and are affected by the viral infection and inflammatory changes in the blood (Pugin et al. 2020). Patients with underlying brain disorders and metabolic derangements are at higher risk for delirium during hospitalization, because in addition to critical illness, there are environmental factors such as unfamiliar surroundings, lack of visitation, uncertainty, and anxiety. These “mental status changes” are likely due to effects of systemic chemical and inflammatory alterations, disruption of neurovascular unit, and the effects of general medical illness on the brain (Fig. 4). It is not clear whether long-term effects of COVID-19 on the nervous system are different from neuropsychiatric manifestation of other severe illnesses.

Neuroimaging studies of COVID-19 patients with neuropsychiatric symptoms reveal non-specific and variable changes in the brain (Kandemirli et al. 2020; Mahammedi et al. 2020). Magnetic resonance imaging data demonstrate lesions in the cortical white matter that are consistent with disruption of neurovascular unit and vasogenic edema (Mahammedi et al. 2020) and endothelialitis of cerebral vessels (Pugin et al. 2020).

Summary

At this juncture, enough molecular and organizational knowledge is available from different disciplines for us to infer some of the mechanisms of injury to human nervous systems by *SARS-CoV-2* that can help in diagnosis and treatment of neurological manifestation of this disease. As more data become available, we will gain a more nuanced clarity regarding neuro-patho-physiology and genesis of COVID-19. *SARS-CoV-2* is a highly adaptable zoonotic virus that uses *ACE2* as an entry receptor into the host cells. Thus, presence of a

functioning *ACE2* protein on the exposed epithelial cells is responsible for the site of initial infection and the phenotype of COVID-19 clinical manifestation. The glycoprotein-studded viral envelope renders the virus agile and adaptable (Li et al. 2020; Korber et al. 2020). As such, *SARS-CoV-2* will likely persist beyond the current pandemic requiring worldwide augmentation of clinical capacity for treatment. A detailed understanding of its mode of infection will assist us in devising appropriate therapies to mitigate neurological effects of the disease.

Loss of sense of taste and smell is an initial symptom of COVID-19 because the virus enters the nasal and oral cavities first and the epithelial cells are the receptors for these senses. COVID-19-associated stroke occurs because of likely injury to vascular endothelial cells and coagulopathy that then cause thrombo-embolism. Encephalopathy in acute and convalescent COVID-19 patients is multifactorial and likely secondary to hypoxia as well as metabolic and immunological abnormalities. Thus far, there is no clear evidence that coronaviruses cause inflammatory neuromuscular diseases via direct invasion of peripheral nerves or muscles or via molecular mimicry. It appears that neurologic injuries in COVID-19 patients are likely indirect and a bystander injury, since *SARS-CoV-2* does not have tropism for the neural cells and tissues.

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