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COVID-19: Viral Life Cycle, Pathogenesis and Neurological Complications

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ABSTRACT

Severe Acute Respiratory Syndrome coronavirus 2 (SARS-CoV-2) is a positive-sense RNA enveloped virus. It is characterized by club-like spikes that form unusually large RNA genomes from their surface and are a unique replication strategy. SARS-CoV-2 causes several diseases and distress in human and potentially fatal respiratory infections. COVID-19 caused by SARS-CoV-2 is a pandemic disease which has led to a global health crisis resulting in millions of deaths worldwide. The following is a brief introduction to the SARS-CoV-2, particularly discussing its replication, pathogenicity, and neurological complications.

Keywords
COVID-19, SARS-CoV-2, Nidovirales, RNA enveloped virus, neurological complications

Introduction

Coronavirus disease was first identified in 1931 when the first human coronavirus HCoV-229E was isolated from a patient in 1965 (Vassilara et al., 2018). Coronavirus disease 2019 (COVID-19) is a current pandemic infection caused by a positive-sense RNA coronavirus. Initially, the virus was called 2019-nCoV (M. Wang et al., 2020). Subsequently, the name of the virus "severe acute respiratory syndrome coronavirus 2" (SARS-CoV-2) was suggested by *Coronaviridae*Study group (CSG Coronaviridae Study Group, 2020). With regard to clinical manifestation, patients with COVID-19 have been reported to suffer from fever, cough, shortness of breath, muscle aches, confusion, dizziness and headache (J. Chen et al., 2020; Nie et al., 2020), sore throat, chest pain, diarrhea, nausea, vomiting (N. Chen et al., 2020; Guo et al., 2020; Mohammed et al., 2020), dyspnea and hemoptysis (SafaaNajah Saud; Al-Humairi et al., 2020; Huang et al., 2020). Multiple organ failure and acute respiratory distress syndrome (ARDS), with the heart being the second damaged organ, has been reported as well (J. Chen et al., 2020).

COVID-19 started as a zoonotic disease, where many animals are reported as the primary reservoir (Lu et al.; Rothan&Byrareddy, 2020). However, there is convincing evidence identifying bats as the natural reservoir of many mammalian coronaviruses, including the SARS-CoV-2 (Rothan&Byrareddy, 2020), SARS-CoV (Lau et al., 2005; Li et al., 2005) and MERS-CoV (Memish et al., 2013). It is highly contagious in humans, particularly among the elderly and people with primary diseases (D. Wang et al., 2020). SARS-CoV-2 is transmitted via direct contact with the infected patient or indirect contact through touch as well as contact with the patient's respiratory droplets (World Health Organization, 2020b). In addition, there are reports that it could also potentially be airborne (S.N.S. Al-Humairi et al., 2020; World Health Organization, 2020a).

SARS-CoV-2 is an enveloped, non-segmented positive-sense RNA virus belonging to the *Nidoviralesorder*, as shown in Figure 1. *Nidovirales* comprises of four families, including the

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families *Arteriviridae*, *Coronaviridae*, *Mesoniviridae*, *and Roniviridae(Cong et al., 2017).* The family *Coronavirinae*includes one of two subfamilies, such as *Coronaviridae* and *Torovirinae*. The family *Coronavirinae* is in addition, subdivided into four categories: Alpha, Beta, Gamma and Delta coronaviruses (de Groot et al., 2012; Siddell, 1995). *Coronavirinae* is known for having the most abundant RNA genome, 27–32kb in size (Fehr & Perlman, 2015; Strauss & Strauss, 2008). SARS-CoV-2, SARS-CoV, MERS-CoV, including HCoV-OC43 and HCoV-HKU1, are human coronaviruses belonging to the genus Betacoronavirus, whereas others, such as HCoV-229E and HCoV-NL63, fit into the Alphacoronavirus genus (Gorbalenya et al., 2006). Animal coronavirus from the genus Alphacoronavirus and Betacoronavirus are mainly associated with mammal infections, whereas viruses of the Gammacoronavirus and Deltacoronavirus genera mostly infect birds (Fehr & Perlman, 2015; Jin et al., 2020; Nakagawa et al., 2016).

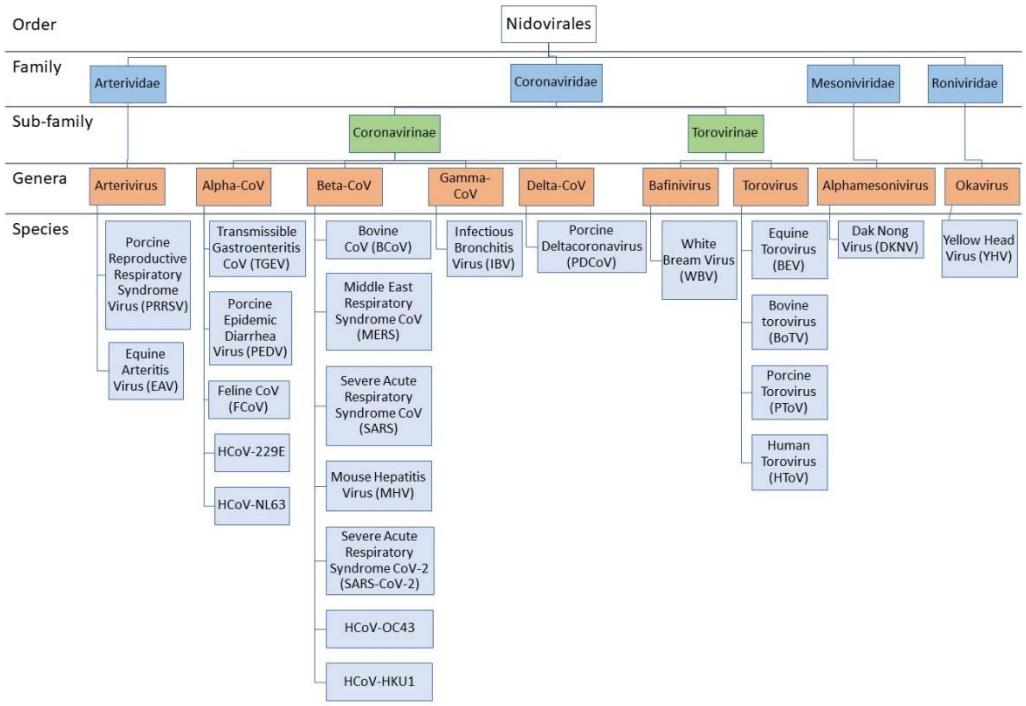

Figure 1.Taxonomy of the enveloped, non-segmented positive-sense RNA virus of *Nidoviralesorder*.

The SARS-CoV-2 complete genome sequence for the first time was deposited in the NCBI (GenBank: MN908947.3) on the 25th January 2020 (Vankadari&Wilce, 2020). This has provided valuable information on the likely structure of the viral proteins and host-virus interaction approach.

The coronavirus virus particles contain four major structural proteins, as shown in Figure 2. These proteins which are encoded at the 3′ end are the S (spike), M (membrane), E (envelope), and N (nucleocapsid) proteins (Beniac et al., 2006; Korsman et al., 2012). The M protein is a small protein (~25–30 kDa) having three transmembrane domains and is the most abundant structural protein which gives the virion its shape (Armstrong et al., 1984). The E protein (~8–12 kDa) is highly divergent with a typical architecture. However, it is found in small quantities within virion(Godet et al., 1992). The N protein is composed of two separate domains (N-

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terminal and C-terminal) and is the only protein in the nucleocapsid(Chang et al., 2006; Kumar, 2020b; Kumar et al., 2020).

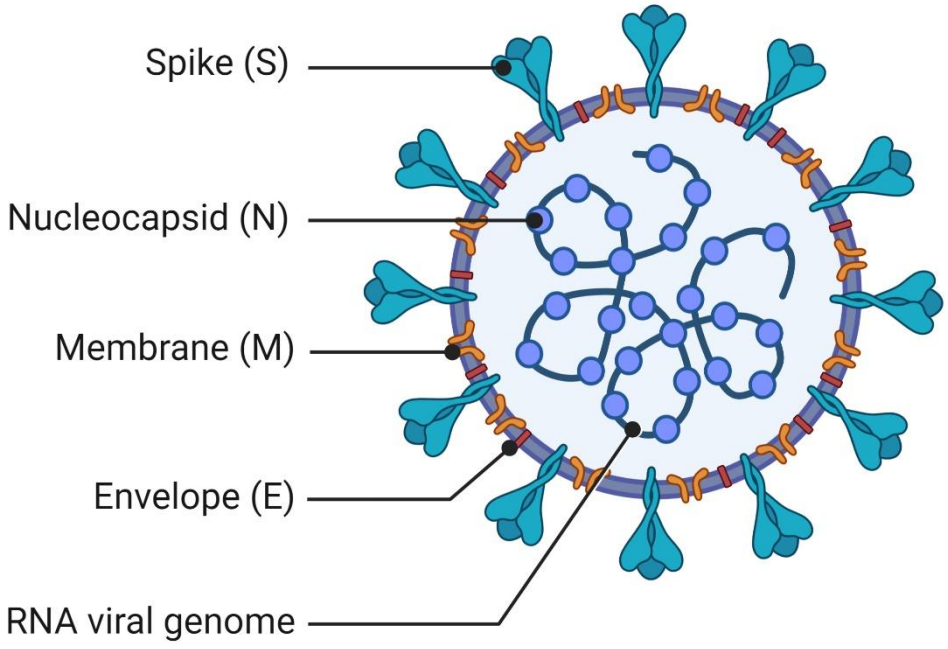

Figure 2.Schematic representations of SARS-CoV-2.N, nucleocapsid protein; S, spike protein; M, membrane protein; E, envelope protein. *Created with BioRender

Viral replication

The viral replication feature of SARS-CoV-2 significantly resembles that of SARS CoV. The SARS-CoV-2 enters the respiratory tract and replicates on the epithelial cells of the respiratory tract (Korsman et al., 2012). The virus S proteins bind to type II pneumocytes receptor known as angiotensin-converting enzyme type 2 (ACE-2) (Patel &Verma, 2020; Y. Wan et al., 2020; Xu et al., 2020) and release its positive single-stranded RNA (+ssRNA) in the cytoplasm.

After penetration and uncoating are completed, the ssRNA is translated into two primary proteins. One inhibits the RNA synthesis in the host cell, and the other is RNA-dependent RNA polymerase (RdRp), which is an enzyme that is needed in order to transcribe the RNA. RdRp copies the virus sense strand (+strand) and makes an antisense strand (−strand), which assists in producing additional +strands (teVelthuis, 2014). The +strands may play the role of mRNA during the translation of subgenomic (nested) mRNA. Viral structural proteins translation occurs at the double-membrane vesicles deriving from the endoplasmic reticulum (ER) membranes (Neuman et al., 2014). Synthesized structural proteins (S, E and M) would combine with nucleocapsid to form a new maturated virion (see in Figure 3).

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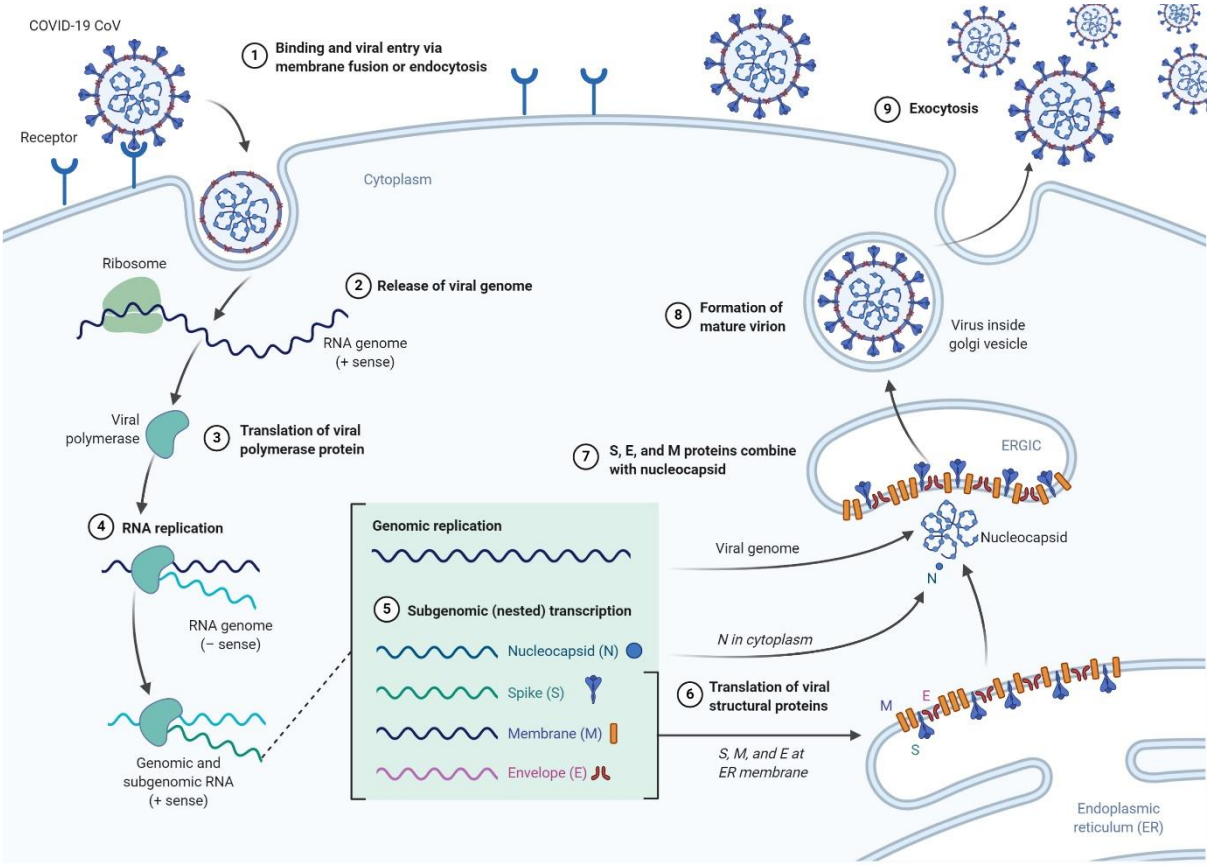

Figure 3.Generalization of SARS-CoV-2 life cycle based on the information acquired by studying SARS-CoV. *Created with BioRender.

Pathogenesis

Once the virus gets in the lower respiratory tract, it starts to attack the alveoli by attaching to type II pneumocytes. The infected type II pneumocytes will trigger the release of neutrophils and inflammatory mediators which subsequently leads to macrophage stimulation leading to cytokine production IL-1β, IL-2R, IL-6, IL-8, IL-10, TNF-α, IFN-α, and IFN-γ (Gong et al., 2020; Kumar, 2020a).

An uncontrolled release of cytokine (cytokine storm syndrome) is very likely to cause acute respiratory distress syndrome (ARDS) in COVID-19 patients (Zhou et al., 2020). Cytokines are released into the blood vessel and cause the endothelial cells of the blood vessel to undergo dilation, which results in an increase in capillary permeability as well as an increase of fluid into interstitial spaces. Neutrophils will rush to the site of infection in the alveoli and try to destroy the virus by releasing Reactive Oxygen Species (ROS) and proteases, which leads to the damage of type I & II pneumocytes as well as alveolar collapse (Reinoso-Vizcaino et al., 2019). This virus subsequently leads to an increasing difficulty to breathe, which in turn results in hypoxemia and ARDS.

The increase in IL-1, IL-6 and TNF-alpha induces the release of prostaglandin E2 which will help to reset the thermostat and increase the body temperature, causing fever to develop (Ye et al., 2020). The decrease in T cell counts of CD4+, CD8+ and increase in the cytokine production IL-1β, IL-2R, IL-6, IL-8, IL-10, TNF-α, IFN-α, and IFN-γ have been frequently reported in COVID-19 severe ARDS cases (Gong et al., 2020; Liu et al., 2020; Wan et al., 2020).

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Intensive and Neurological Complications

With regard to the similarity between SARS-CoV and SARS-CoV-2, both viruses have also shown a similar invasive mechanism in some patients. The two pathways which have been described that lead to neuro-invasion are the hematogenous route and the retrograde axonal transport route through the cranial nerves that display ACE-2-Receptor such as trigeminal, glossopharyngeal, and vagus nerves; this marks the onset of brain involvement (Guan et al., 2020).

The ACE-2-Receptor is an integrated membrane glycoprotein, which is expressed in the lungs, endothelium, heart, and kidneys. The downregulation of these receptors causes increased susceptibility for lung injury (Kuba et al., 2006).

An alteration of the sense of smell or hyposmia has been described to have occurred in early-stage COVID-19 patient with no severe complications (Baig et al., 2020). Studies on mice showed that following an intranasal virus inoculation, SARS-CoV-2 has the potential to invade the brain through the olfactory epithelium and cause neuronal death (Baig et al., 2020; D. Wang et al., 2020). In one study with the Mice Transgenic for Human ACE-2-receptor infected with SARS-CoV, it was shown that the brainstem, more precisely the solitary nucleus (SN), area postrema, and dorsal motor nucleus of the vagus nerve, was infected in all four samples examined (Baig et al., 2020). Baig et al. (2020 also reported that the areas of the cortex (piriform and infralimbic cortices), basal ganglia (ventral pallidum and lateral preoptic regions), and midbrain (dorsal raphe) to have been highly infected. In a cross-sectional study conducted post-viral epidemic, olfactory dysfunction has been reported with a sudden onset of anosmia, constant decrease in the sense of smell as well as a decrease in the taste sensation (Bagheri et al., 2020).

In most cases, patients experience mild symptoms such as fever, cough, headache, myalgia, dyspnea, and anosmia. However, others might develop acute respiratory distress syndrome approximately a week after the onset of the disease, which may eventually result in death (with 21 days median time from onset to death) (J. Chen et al., 2020). As opposed to individuals infected with SARS CoV, those infected with SARS-CoV-2 seldom display prominent upper respiratory tract signs and symptoms, which indicates that the target cells of SARS-CoV-2 may be present in the lower airway (N. Chen et al., 2020). Based on imaging examination performed on patients, chest computerized tomography scans displayed bilateral ground-glass opacities among those with fever, dry cough, and dyspnea (Huang et al., 2020).

Deaths from circulatory failure with myocardial damage as well as fulminant myocarditis have been reported as a consequence of cytokine storm (N. Chen et al., 2020). T. Chen et al. (2020) observed 113 common patients with the following complications that lead to death: acute cardiac injury with heart failure, acute respiratory distress syndrome, acute kidney injury, sepsis, and hypoxic encephalopathy. The likelihood to develop complications was higher among patients with cardiovascular comorbidity. Less common complications included disseminated intravascular coagulation, acidosis, and acute liver injury. In addition, a patient who died was reported to have developed gastrointestinal bleeding (T. Chen et al., 2020).

Cerebrovascular disease, consciousness impairment, and muscle injury were reported in 78 COVID-19 cases with severe symptoms (Mao et al., 2020).

Previous studies have shown that SARS-CoV-2 was found in the CSF of infected patients and thus causing encephalitis with status epilepticus(Arabi et al., 2015). However, CSF analysis in COVID-19 patients has not been reported due to limitations in traumatic lumbar puncture (Poyiadji et al., 2020).

In comparison with SARS-CoV, acute necrotizing encephalopathy (ANE) has been identified in COVID-19 patients. Cranial MRI has shown a haemorrhagic enhancing rim lesion within

bilateral thalami, medial temporal lobes and subuinsular regions, just as computed tomography has shown asymmetric hypoattenuation in the bilateral medial thalami (Poyiadji et al., 2020).
Severe acute disseminated encephalomyelitis has been reported in many cases with HCoV-OC43 and MERS-CoV infections (Arabi et al., 2015; Kim et al., 2017; Yeh et al., 2004). Neurological symptoms such as Bickerstaff's encephalitis overlapping with Guillain-Barré/Miller-Fischer-Syndrome, critical-illness syndromes or other toxic neuropathies have been reported during and post-MERS-CoV treatment (Kim et al., 2017). A case with Guillain-Barré syndrome was seen among COVID-19 patients in Shanghai which showed a pattern of a para-infectious profile, where the patient had developed a fever and respiratory symptoms seven days after the outset of Guillain-Barré-Syndrome (Zhao et al., 2020).

Conclusion

Similar to MERS-CoV and SARS-CoV, the SARS-CoV-2 has the potential to cause similar disease patterns and complications. Although it starts as an influenza-like disease, it could progress to severe respiratory disorders, eventually leading to death. Its transmission and spreading capacity have surpassed that of all other coronaviruses. Individuals with no symptoms have shown the ability to transmit the disease, thus increasing the number of infections and making it difficult to control the pandemic outbreak.
Much remains to be understood regarding the SARS-CoV-2 neurological implications, and whether the brainstem involvement leads to the cardiorespiratory complications or vice versa still warrants future research. To understand the viral impact, brain imaging and pathological evaluations are needed.

Competing interests

The authors declare that they have no competing interests.

Author's contributions

A.Z. and A.B. contributed substantially to the conception and design of the study, the acquisition of data, or the analysis and interpretation. Both authors participated in the writing of the article.

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