Novel Coronavirus: What Neuroradiologists as Citizens of the World Need to Know

ⓘ A. Mahajan and ⓘ J.A. Hirsch

In December 2019, a novel β-coronavirus, initially called severe acute respiratory syndrome–coronavirus 2 (SARS-CoV-2) was introduced into the human population.[1] It is spreading rapidly. The World Health Organization has labeled the disease Coronavirus disease 2019 (COVID-19). This constitutes the seventh member of the Coronaviridae family known to infect humans, which includes the SARS and the Middle East Respiratory Syndrome (MERS) viruses. Considering the close identity of the virus with one found in bats, the disease is considered to be a zoonosis, ie, a disease that can be transmitted from animals to humans. The disease was declared a pandemic on March 11, 2020.

In this era of 24/7 news coverage available across much of the globe, people are watching the epidemic unfold in nearly real-time. This situation creates a unique dynamic in that for the first time ever, the global community is learning about this disease as it develops. Unfortunately, there is much misinformation that contributes to an overall climate of fear. The disease in question may not, for example, be as deadly as recent pandemics, eg, the Ebola virus. Simultaneously, we see an interplay between those who tend to play down the seriousness of the disease while there are those who are preparing for the worst with hoarding.

Neuroradiologists, as medical providers, are expected to provide guidance to the general public. Having the best available information will help us take better care of our families, friends, patients, and ourselves. In that context, it becomes imperative for neuroradiologists to learn as much as possible about this virus to educate the public about this entity.

The COVID-19 virus is an enveloped RNA virus with a single-strand, linear, positive-sense RNA, which means that the virus can use its RNA as the template from which to create proteins needed for propagation and spread. The genome length is 29,903 bases.[2] The virus was initially labeled as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) due to its phylogenetic similarity to SARS-CoV (80% identical); however, it was more similar to the bat coronaviruses (96% identical).[3]

The name "coronavirus" refers to the crownlike appearance of these viruses seen on electron microscopy. The virus is around 70–220 nm in size. It is similar to the SARS-CoV regarding the mode of entry and the human receptor used for entry. The infectiousness of the virus is unclear but appears to be more infectious than SARS and MERS viruses, though less fatal.[4]

The virus gains entry into the cell after binding of the spike protein (S) on its surface with the angiotensin-converting enzyme 2 (ACE-2) on the surface of the host cell.[5] The S-protein interaction with ACE-2 appears to be essential for entry of the virus into the cell and is a candidate for vaccine development. The SARS-CoV spike (S) protein is composed of 2 subunits: The S1 subunit contains a receptor-binding domain that binds to the host cell receptor and the S2 subunit mediates fusion between the viral and host cell membranes.[6] None of the commercially available ACE inhibitors are effective against the ACE-2 enzyme. The neutralizing antibodies to the SARS-CoV bind to the ACE-2 receptor binding domain (RBD) of the SARS S-protein, highlighting the importance of this protein for virus entry. Although there is only 76.5% identity of amino acid sequences between COVID-19 and SARS-CoV, suggesting a difference in the RBD of SARS-CoV and COVID-19 viruses, they have almost identical 3D structures in the RBD with a strong binding to human ACE-2.[7] Active vaccine development against the S-protein is in progress currently.

The ACE-2 enzyme is involved with the degradation of angiotensin-II in the renin angiotensin system. Whether the interaction of the virus with angiotensin-II is important in the pathogenesis of COVID-19 is unknown. Most interesting, the ACE-2 expression is seen predominantly in the respiratory and intestinal tracts, which are the 2 sites of involvement of the coronavirus. In the respiratory epithelium, the ACE-2 was expressed in human airway epithelia as well as the lung parenchyma. ACE-2 may have a protective effect on the lung parenchyma, with alterations in the renin angiotensin system as the putative mechanism of lung injury.

The transmission of the coronavirus occurs via droplets and fomites during close unprotected contact. Fomites are objects or materials that are likely to carry infection, such as clothes, utensils, and furniture. Fecal shedding has been demonstrated, but fecal-oral transmission is not considered a driver of the epidemic. Aerosolization of fomites may contribute to airborne transmission, though currently this mode is not considered too important in the community. Transmission has been documented in the preclinical stage as well, even before the onset of symptoms.[8] Asymptomatic carriers as well as a prolonged incubation period up to 19 days has also been described, though reinfection may be another possibility in this case.[9]

The incubation is reported to be 2–7 days.[10] After virus isolation in various cell lines in vitro, cytopathic effects were observed 96 hours after inoculation. Whole genome sequencing of 104 strains of the virus from different locations around the globe reveals a 99.9% homology.

The severity of clinical symptoms may vary from

- Mild to moderate in 80%; most recover
- Severe in 13.8% (dyspnea, respiratory rate > 30/min, O_2 saturation ≤ 93%, partial pressure of oxygen/fraction of inspired oxygen ratio < 300, lung infiltrates >50% of the lung within 24–48 hours)
- Critical in 6.1% (respiratory failure, septic shock, and/or multiorgan dysfunction/failure).

Fever was the most common symptom seen in 89% of 1099 hospitalized patients in China,[10] though seen at initial presentation in only 44%. Sore throat was seen in only 14%; nasal congestion, in 5%; but cough, in 68%. Dyspnea may be a more serious presentation with severe acute respiratory distress syndrome seen in 17%–29%.[11] The time from onset to the development of severe disease, including hypoxia, is 1 week. There was no sex predilection. Among patients who have died, the time from symptom onset to death ranged from 2–8 weeks. Individuals at highest risk of severe disease and death include those older than 60 years of age and those with underlying conditions such as hypertension, diabetes, cardiovascular disease, chronic respiratory disease, and cancer.

The disease in children appears to be relatively rare and mild, with approximately 2.4% of the total reported cases among individuals younger than 19 years of age. A very small proportion of those younger than 19 years of age have developed severe (2.5%) or critical disease (0.2%).

The diagnosis is based on reverse transcription polymerase chain reaction (RT-PCR) of throat (oropharyngeal) and nasopharyngeal swabs, though sputum and bronchoalveolar lavage fluid had the best sensitivity. However, reports from China indicate that the RT-PCR sensitivity may have been as low as 60%–70%.[12]

Temporal changes seen on chest CT findings have been described by a panel of experts:[13] These included lack of abnormality in the first 2 days of illness in 50%. In early disease, peripheral, focal, or multifocal ground-glass opacities, affecting both lungs, may be seen in approximately 50%–75% of patients. With the progression of disease, crazy paving (ground-glass opacities with interlobular septal thickening) and consolidation became prominent, with a peak around 9–13 days, followed by slow clearing during a month or longer.

Chest CT was reported as better than RT-PCR in a recent article in *Radiology*.[12] Closer analysis of the data reveals that most patients with chest CT scans demonstrating lung pathology but PCR negative for COVID-19 were diagnosed on clinical grounds alone. However, only 15 cases had a positive PCR result on repeat testing. The PCR-negative patients with a positive CT result may reflect viral pneumonia related to other respiratory viruses, common during this time of the year. Chinese authorities had initially broadened the official definition of infection in Hubei province to include patients with typical findings of viral pneumonia on CT, with negative RT-PCR results. This inclusion caused a spike of 13,332 cases on February 12. This broader definition resulted in a higher number of presumptive cases of COVID-19 in China with a recommendation for a role for chest CT in the initial diagnosis of COVID-19 infection versus RT-PCR. However, chest CT was removed as a diagnostic criterion in the sixth version of the diagnostic criteria published on February 16, 2020.[14] RT-PCR remains the reference standard to make a definitive diagnosis of COVID-19 infection.[15]

Chest x-ray and chest CT may be used as adjuncts in case an initial RT-PCR has negative findings. The American College of Radiology[16] warns against using CT as a first-line tool in the diagnosis of coronavirus and it should be used sparingly and reserved for symptomatic hospitalized patients with specific clinical indications. Using portable radiography may be helpful, considering the ease of cleaning. CT scanners may need to be closed for an extended period—up to 1 hour after scanning a suspected patient—for cleaning and decontamination, affecting overall patient care.[17]

Remdesivir and chloroquine have shown efficacy in vitro.[18] Remdesivir inhibits the RNA-dependent RNA polymerase, essential for replication of the virus.[19] Chloroquine has shown apparent efficacy in the treatment of COVID-19–associated pneumonia in studies from China.[20] It supposedly exerts its antiviral activity, in part, by interfering with cell fusion by increasing endosomal pH, interfering with virus/cell fusion, and interfering with the glycosylation of cellular receptors of SARS-CoV. Clinical trials are underway, the results of which may be available in April. Recombinant ACE-2 trials are also underway (ClinicalTrials.gov NCT04287686).[5] A host of drugs being tested include interferon β; an HIV drug, lopinavir-ritonavir (Kaletra); and neuraminidase inhibitors like oseltamivir, among others.[21]

Vaccine development is also underway. Most promising is the vaccine targeting the spike protein (S). The molecule has been isolated, and the structure, elucidated.[22] First clinical trials of a mRNA based vaccine started on March 16, 2020 in Seattle though results may be months away.

The mortality rate was estimated at 3%–4%, though more recent estimates suggest 0.3%–1%; however, the risk to the immunosuppressed and the elderly is of great concern in the United States, especially with a large population of immunosuppressed patients and those on various immunosuppressive medications for a host of conditions. In a study of 1044 hospitalized patients in China, a mortality rate of 1.4% was identified,[10] which may have been lower if patients with fewer symptoms from the community had been included.

Infection control measures for health care professionals when coming in contact with infected individuals especially those performing lumbar punctures, myelograms and spine procedures in the neuroradiology community, should include contact and airborne precautions, which include hand hygiene, gloves, gowns, N95 masks, and eye protection. During the SARS epidemic, the hospital personnel who became infected had omitted at least one of these precautions.[23] There was no difference between using a surgical mask and a N95 mask in this case-control study from Hong Kong. Footwear protection should also be considered. More detailed instructions for use in the radiology department have recently been published.[24] An analysis of 22 studies[25] revealed that human coronaviruses such as SARS, MERS, or endemic human coronaviruses can persist on inanimate surfaces like metal, glass, or plastic for up to 9 days but can be efficiently inactivated by surface disinfection procedures with 62%–71% ethanol, 0.5% hydrogen peroxide, or 0.1% sodium hypochlorite within 1 minute of application, whereas 0.05%–0.2% benzalkonium chloride or 0.02% chlorhexidine digluconate are less effective.

Infection control measures like voluntary and mandated quarantine at an individual, community, national, and international level may ultimately be the only plausible way of controlling the spread of the disease.[26] These measures do work, as evidenced by the marked decrease in the incidence of cases from China.[27] On

an individual level, social distancing, self-isolation at the first appearance of symptoms, contact tracing, and informing the contacts may be the best measures to effectively control the spread of the disease. Availability of suitable testing methods may also go a long way to ensure peace of mind to the public at large.

In conclusion, in the midst of an ongoing epidemic, it is best to obtain as much information as we can about this virus so that we can take effective care of the community around us.

REFERENCES

1. 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 CrossRef Medline
2. **Report of the WHO-China Joint Mission on Coronavirus Disease 2019 (COVID-19).** February 16-24, 2020. https://www.who.int/docs/default-source/coronavirus/who-china-joint-mission-on-covid-19-final-report.pdf. Accessed March 12, 2020
3. Zhou P, Yang XL, Wang XG, et al. **A pneumonia outbreak associated with a new coronavirus of probable bat origin.** *Nature* 2020;579:270–73 CrossRef Medline
4. Chen J. **Pathogenicity and transmissibility of 2019-nCoV:a quick overview and comparison with other emerging viruses.** *Microbes Infect* 2020 Feb 4. [Epub ahead of print] CrossRef
5. Zhang H, Penninger JM, Li Y, et al. **Angiotensin-converting enzyme 2 (ACE2) as a SARS-CoV-2 receptor: molecular mechanisms and potential therapeutic target.** *Intensive Care Med* 2020 Mar 3. [Epub ahead of print] CrossRef Medline
6. Du L, He Y, Zhou Y, et al. **The spike protein of SARS-CoV: a target for vaccine and therapeutic development.** *Nat Rev Microbiol* 2009;7:226–36 CrossRef Medline
7. Tian X, Li C, Huang A, et al. **Potent binding of 2019 novel coronavirus spike protein by a SARS coronavirus-specific human monoclonal antibody.** *Emerg Microbes Infect* 2020;9:382–85 CrossRef Medline
8. Rothe C, Schunk M, Sothmann P, et al. **Transmission of 2019-nCoV infection from an asymptomatic contact in Germany.** *N Engl J Med* 2020;382:970–71 CrossRef Medline
9. Bai Y, Yao L, Wei T, et al. **Presumed asymptomatic carrier transmission of COVID-19.** *JAMA* 2020 Feb 21. [Epub ahead of print] CrossRef Medline
10. Guan WJ, Ni ZY, Hu Y, et al. **Clinical characteristics of coronavirus disease 2019 in China.** *N Engl J Med* 2020 Feb 28. [Epub ahead of print] CrossRef Medline
11. 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 CrossRef Medline
12. Ai T, Yang Z, Hou H, et al. **Correlation of chest CT and RT-PCR testing in coronavirus disease 2019 (COVID-19) in China: a report of 1014 cases.** *Radiology* 2020 Feb 26. [Epub ahead of print] CrossRef [Medline
13. Kanne JP, Little BP, Chung JH, et al. **Essentials for radiologists on COVID-19: An Update—Radiology Scientific Expert Panel.** *Radiology* 2020 Feb 27. [Epub ahead of print] CrossRef Medline
14. Jin YH, Cai L, Cheng ZS, et al; Zhongnan Hospital of Wuhan University Novel Coronavirus Management and Research Team, Evidence-Based Medicine Chapter of China International Exchange and Promotive Association for Medical and Health Care (CPAM), **A rapid advice guideline for the diagnosis and treatment of 2019 novel coronavirus (2019-nCoV) infected pneumonia (standard version).** *Mil Med Res* 2020;7:4 CrossRef Medline
15. Yang W, Yan F. **Patients with RT-PCR confirmed COVID-19 and normal chest CT.** *Radiology* 2020 Mar 6. [Epub ahead of print] CrossRef Medline
16. **ACR recommendations for the use of chest radiography and computed tomography (CT) for suspected COVID-19 infection.** March 11, 2020. https://www.acr.org/Advocacy-and-Economics/ACR-Position-Statements/Recommendations-for-Chest-Radiography-and-CT-for-Suspected-COVID19-Infection. Accessed March 12, 2020
17. Stempniak M. **CT should not be used as first-line tool against coronavirus, ACR warns following pandemic declaration.** *Radiology Business*. March 11, 2020. https://www.radiologybusiness.com/topics/care-delivery/ct-scan-coronavirus-chest-x-ray-radiology-covid-19. Accessed March 12, 2020
18. Wang M, Cao R, Zhang L, et al. **Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro.** *Cell Res* 2020;30:269–71 CrossRef Medline
19. Gordon CJ, Tchesnokov EP, Feng JY, et al. **The antiviral compound remdesivir potently inhibits RNA-dependent RNA polymerase from Middle East respiratory syndrome coronavirus.** *J Biol Chem* 2020 Feb 24. [Epub ahead of print] CrossRef Medline
20. Gao J, Tian Z, Yang X. **Breakthrough: Chloroquine phosphate has shown apparent efficacy in treatment of COVID-19 associated pneumonia in clinical studies.** *Biosci Trends* 2020 Feb 19. [Epub ahead of print] CrossRef Medline
21. Lu H. **Drug treatment options for the 2019-new coronavirus (2019-nCoV).** *Biosci Trends* 2020 Jan 28. [Epub ahead of print] CrossRef Medline
22. Wrapp D, Wang N, Corbett KS, et al. **Cryo-EM structure of the 2019-nCoV spike in the prefusion conformation.** *Science* 2020;367:1260–63 CrossRef Medline
23. Seto WH, Tsang D, Yung RW, et al; Advisors of Expert SARS group of Hospital Authority. **Effectiveness of precautions against droplets and contact in prevention of nosocomial transmission of severe acute respiratory syndrome (SARS).** *Lancet* 2003;361:1519–20 CrossRef Medline
24. Kooraki S, Hosseiny M, Myers L, et al. **Coronavirus (COVID-19) outbreak: what the department of radiology should know.** *J Am Coll Radiol* 2020 Feb 19. [Epub ahead of print] CrossRef Medline
25. Kampf G, Todt D, Pfaender S, et al. **Persistence of coronaviruses on inanimate surfaces and their inactivation with biocidal agents.** *J Hosp Infect* 2020;104:246–51 CrossRef Medline
26. Anderson RM, Heesterbeek H, Klinkenberg D, et al. **How will country-based mitigation measures influence the course of the COVID-19 epidemic?** *Lancet* 2020 March 6. [Epub ahead of print] CrossRef Medline
27. World Health Organization. **Coronavirus Disease 2019 (COVID-19) Situation Report—44.** March 4, 2020. https://www.who.int/docs/default-source/coronavirus/situation-reports/20200304-sitrep-44-covid-19.pdf?sfvrsn=93937f92_6. Accessed March12, 2020