Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Sleep Medicine 72 (2020) 164–166

Contents lists available at ScienceDirect

Sleep Medicine

journal homepage: www.elsevier.com/locate/sleep

Editorial

The many faces and fangs of COVID-19: an editorial by Sudhansu Chokroverty

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was originally identified by the International Committee on Taxonomy for Virus (ICTV). On February 17th 2020, the World Health Organization (WHO) named the disease associated with the virus SARS-CoV-2 the 2019 novel strain of coronavirus (COVID-19). By March 11, 2020 the WHO declared COVID-19 (which affects predominantly the respiratory tract, at least initially) to be a pandemic. This cataclysmic, highly contagious and devastating condition is reminiscent of the 1918 influenza pandemic (also known as the "Spanish Flu") caused by an unknown influenza virus which was later identified in 1933 after analyzing viral RNA sequences in the postmortem tissues obtained from the victims. The 1918 influenza pandemic was believed to have started in Romania in 1915. It lasted approximately 10 years and killed over 50 million people worldwide [1]. Based on the astute clinico-pathological observations of the smart young Australian Neurologist, Constantin von Economo, knowledge about anatomical substrates of sleep-wake states greatly increased.

In the 21st century, COVID-19 has become a vast destroyer of human health and economy, and may be considered as the greatest global public health crisis today. The condition was first documented sometime in late December 2019 (although some say as early as November 17th, 2019) in the city of Wuhan, located in the Hubei province of China. COVID-19 then spread rapidly across China, other parts of South-East Asia, and eventually globally; maximally affecting the USA and Europe. According to the WHO, as of June 1st 2020 COVID-19 has affected over six million (6,057,853) people worldwide, killing over 370,000 (371,166) including over one million (1,734,040) affected individuals in the United States with a death count of 102,640 people.

Much about this novel virus currently remains unknown, including i. the nature of its invasion of the human mind and body; ii. its pathophysiological mechanism; iii. the long-term natural history of COVID-19; and iv. the burden of the disease involving multiple organs [2–4]. The clinical spectrum is still evolving [5–12]. We do know it severely affects the vulnerable elderly population and those with significant comorbidities with high mortality. Children may develop pediatric multisystem inflammatory syndrome resembling Kawasaki disease (a rare condition also known as mucocutaneous lymph node syndrome) which may be a rare complication of COVID-19 associated with high fatalities. The pathogenesis of this highly contagious COVID-19 remains uncertain. It appears that the virus invades angiotensin converting enzyme (ACE) receptor 2 (ACE-R2) causing damage to the endothelium (endothelialitis) promoting thrombosis in multiple organs and systems of the body (eg, brain causing stroke and other central nervous system [CNS] as well as peripheral nervous system [PNS] damage, and possibly also affecting the autonomic nervous system [ANS] causing dysautonomia) and other organs (see further on) [10,12–14].

The initial manifestation of COVID-19 may be mild with fatigue, fever (in about 50%), dry cough, sore throat, runny nose with sneezing, diffuse myalgia, nonspecific chest pain and shortness of breath. The condition may progress after a variable interval to a moderate-severe state with pneumonia and acute respiratory distress syndrome (ARDS) with progressive hypoxemic respiratory failure requiring admission to the intensive care unit (ICU) and intervention with ventilator associated with increased mortality (about 1% in those without comorbidity and 59% in those with comorbidities). Some cases may remain asymptomatic, although capable of spreading the virus to others. Occasional patients may present with nausea, vomiting and diarrhea. Infrequently, other organs and symptoms (eg, cardiac injury [cardiomyopathy, cardiac arrhythmias, cardiac failure and pericardial effusion], kidney injury causing renal failure, hepatitis and neurological system involvement causing stroke and other manifestations [see further on]). Some important laboratory findings include the characteristic multifocal ground glass appearance of the lungs in the computed tomographic (CT) scan of the chest, leukocytosis with lymphopenia, increased D-dimer blood level (indicating hypercoagulable state), increased troponin 1 (marker of cardiac injury), elevated blood urea nitrogen (BUN) and creatinine (suggesting kidney damage), elevated alanine transaminase (ALT) and other liver enzymes (pointing to liver damage) and increased inflammatory markers in the blood (eg, C-reactive protein [CRP]), and cytokines [may cause cytokine storms]. Pertinent pathological findings obtained at postmortem tissues include evidence of diffuse alveolar disorder (DAD), pulmonary and other vascular endothelialitis, thrombosis, particularly in large vessels and angiogenesis (including microangiopathy) as well as electron-microscopic presence of viral particles in pneumocytes [14–16]. Oxley et al.'s study [16], points to antemortem presentation of stroke due to large vessel thrombosis.

I shall now briefly focus on sleep dysfunction which is frequent and neurological manifestations (infrequent) of COVID-19 based on what is currently known. Sleep is adversely affected not only in patients but also in frontline health care workers (FHCW) directly involved in caring for COVID-19 patients (eg, physicians, nurses and to an extent other paramedical personnel), as well as other HCW involved in caring for non-COVID-19 patients, others in the hospital environment not directly involved in patient care activities, and even in the general population. Sleep dysfunction is common in patients admitted to the ICU (related to many factors) under

https://doi.org/10.1016/j.sleep.2020.06.006

normal circumstances, but is seen more severely in COVID-19 ICU patients and others as well as those in non-COVID-19 units [17–19].

In the acute stage during hospitalization COVID-19 patients often have sleep onset and maintenance insomnia due to sleep deprivation. FHCW may suffer from similar sleep dysfunction which is more marked compared with that in non-FHCW, hospital workers not involved in direct patient care and general population Whether the patients or others will later develop persistent insomnia (chronic insomnia disorder which is different from sleep deprivation related acute insomnia) remains to be studied. There is also a suggestion based on theoretical assumption (no formal studies have been published yet) that there may be an increased incidence and prevalence of obstructive sleep apnea (OSA) in COVID-19 patients through the pathway of ACE-R2 and hypertension as well as increased inflammatory response (eg, increased CRP and cytokine storms [20]). This could be a bidirectional response, ie, COVID-19 may cause an increased incidence of OSA (an undesirable complication of COVID-19) working through the same ACE-R2 and hypertension pathways. Furthermore, management of OSA patients with COVID-19 requires special care and precautions. Whether some COVID-19 patients will develop secondary circadian rhythm sleep disorder (CRSD) as a result of disturbed sleep-wake schedule during hospitalization of these patients in the ICU remains to be studied. Finally, the questions of dream disorder (eg, nightmares related to fear of death and coronavirus related dreadful complications) with or without abnormal behavior remains a possibility but has not been studied yet. Of note, in some COVID-19 patients post-traumatic stress disorder (PTSD)-like symptoms may occur.

It is important to be aware of impaired sleep quality and other sleep dysfunctions not only in patients, but also in HCW, particularly frontline workers because impaired sleep may affect their judgement in patient care and timely investigation may improve sleep and the short as well as long-term consequences of sleep disruption. Scattered case reports, case series, reviews, anecdotal and newspaper announcements attest to the above facts. Several factors may be cited (listed below) to account for sleep dysfunction among HCW, particularly FHCW: i. anxiety; ii. mental stress; iii. fear of contracting this highly contagious condition; iv. fear of transmitting the virus to family members and colleagues; v. uncertainty about the disease; iv. overwhelming workload; vii. inadequate personal protection equipment (PPE) and availability of sufficient number of ventilators (at least in the beginning when first involved in care of COVID-19 positive and confirmed cases); viii. the feeling of being inadequately supported; ix. reluctance to work in this environment with constant fear of coronavirus or even contemplating resignation; x. experiencing high levels of stress and anxiety causing symptoms of depression which may have long lasting psychological implications and even suicidal thoughts; xi. lack of a vaccine or a specific drug treatment; and xii. in some instances, medications and comorbid conditions, which may play a role.

Some COVID-19 patients may have involvement (not common) of CNS, PNS and possibly also ANS either as a result of direct viral invasion or ascent to the brain through the olfactory pathway, or indirectly as a result of systemic increased inflammatory responses and immunological and metabolic dysfunction; as well as hematogenous spread or virus mediated vascular endothelialitis and microangiopathy. CNS manifestations may include headache and dizziness (non-specific), anosmia and ageusia or dysgeusia (about 1% of cases), blurring of vision, facial and other cranial nerve involvement (extent of this is not known as the clinical picture is still evolving), stroke, mostly thrombosis of large vessel in relatively young people [16], but could be thromboembolic and microangiopathic affecting small vessels, cerebellar ataxia, altered state of consciousness and impaired vigilance, confusion and delirium, as well as visual loss and seizures [21,22]. The PNS manifestations may include Guillain-Barre-like syndrome, other neuromuscular disorders (eg, diffuse myalgia or possibly polymyositis and neurogenic pain) [21,22]. No formal studies have been published regarding ANS manifestations but severe hypotension could be related to either dysautonomia or generalized shock related to multiorgan failure.

There are many aspects of COVID-19 that remain undetermined today without further investigations. We do not also have a clear answer to many of the frequently asked questions as follows:

Q.1. Is there a role for a repeat test for a negative COVID-19 case?

A.1. A negative reverse transcriptase (RT) polymerase chain reaction (PCR) test does not necessarily exclude COVID-19 for a variety of reasons. Hence certain individuals may need a repeat RT-PCR swab test [11].

Q.2. Can a patient be re-infected after recovering from COVID-19?

A.2. Although there have been occasional reports from Japan and China this topic remains highly controversial. For a discussion see Omer et al., [11].

Q.3. How long does immunity last after recovery from the first attack of COVID-19?

A.3. At present the answer remains inconclusive [11].

Q.4. Should a patient with hypertension start taking ACE inhibitors or angiotensin receptor blockers (ACB's) when infected with COVID-19?

A.4. This remains controversial. There are arguments for both the use and cessation of these agents [20]. Although ACE-R2 is thought to be a co-receptor for entry of coronavirus into the human body, the joint recommendation decision by the American College of Cardiology and the American Heart Association is to continue taking these medications as prescribed until sufficient evidence is available [20].

Only time will tell whether we will defeat this malignant viral epidemic. Indeed, we have a herculean task ahead of us. What is needed desperately now is an effective vaccine as a prophylaxis to prevent future occurrence as well as an effective treatment. We are making valiant progress in both directions but we are not there yet. Perhaps we will succeed in those endeavors in the early or middle part of the next year (2021). For the sake of our health, humanity, and economy we continue to hope for good news. In the meantime, we must follow the scientific guidelines for precautionary measures (eg, social distancing, wearing face masks, frequent handwashing rituals [excellent hygienic measures], quarantine and wearing gloves if necessary). I must voice a word of caution. It is unfortunate and regrettable that national and international politics are involved in the endeavor ahead of us. A healthy competition is, of course, good for all. There is, however, no room for personal or political advantages in our quest for scientific progress in our understanding of the pathogenesis, the natural evolution of the clinical picture, epidemiological pathway as well as finding an effective vaccine and therapy for COVID-19. Mankind is under attack by an invisible calamitous enemy. Therefore, united, we must follow a course of action which requires collaboration and cooperation. We must destroy the fangs of this monstrous enemy once and for all. The situation is evolving and we remain optimistic. Stay tuned.

Conflict of interest

The ICMJE Uniform Disclosure Form for Potential Conflicts of Interest associated with this article can be viewed by clicking on the following link: https://doi.org/10.1016/j.sleep.2020.06.006.

References

[1] Morens DM, Taubenberger JK. Influenza cataclysm, 1918: perspective. N Engl J Med 2018;379:2285–7.
[2] Lipsitch M, Swerdlow DL, Finelli L. Defining the epidemiology of COVID-19-studies needed. N Engl J Med 2020;382:1194–6.
[3] Hartley DM, Perencevich EN. Public health intervention for COVID-19: emerging evidence and implications for an evolving public health crisis. JAMA 2020;323:1908–9.
[4] Pan A, Liu L, Wang C, et al. Association of public health interventions with the epidemiology of the COVID-19 outbreak in Wuhan, China. JAMA 2020;323:1915–23.
[5] Zhu N, Zhang D, Wang W, et al. A novel coronavirus from patients with pneumonia in China. N Engl J Med 2019. https://doi.org/10.1056/NEJMoa2001017.
[6] Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 2020 January 24 (Epub ahead of print).
[7] Chen N, Zhou M, Dong Jr X, et al. Epidemiological and clinical characteristics of 99 cases of 2019 Novel Coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet 2020 January 30 (Epub ahead of print).
[8] Holshue ML, DeBolt C, Lindquist S, et al. First case of 2019 novel coronavirus in the United States. N Engl J Med 2020;382:929–36.
[9] The Covid-19 Investigation Team. First 12 patients with coronavirus disease 2019 (COVID-19) in the United States. 2020. https://doi.org/10.1101/2020.03.09.20032896.
[10] Bhatraju PK, Ghassemich BJ, Nichols M, et al. COVID-19 in critically ill patients in the Seattle region- case series. N Engl J Med 2020;382:2012–22.
[11] Omer SB, Malani P, del Rio C. The COVID-19 pandemic in the US. A clinical update. JAMA 2020;323:1767–8.
[12] Grasselli G, Zangrillo A, Zanella A, et al. Baseline characteristics and outcome of 1591 patients infected with SARS-COV-2 admitted to ICUs of the Lombardy region, Italy. JAMA 2020;323:1574–81.
[13] Sise ME, Baggett MV, Shepard JO, et al. A man with COVID-19 and acute kidney injury. N Engl J Med 2020;382:2147–56.
[14] Ackerman M, Verleden SF, Kuchnel M, et al. Pulmonary vascular endotheliialitis, thrombosis, and angiogenesis in COVID-19. N Engl J Med 2020 (Published online May 21, 2020).
[15] Wichmann D, Sperhake JP, Kluge S. Autopsy findings and venous thromboembolism in patients with COVID-19. Ann Intern Med 2020. https://doi.org/10.7326/M20-2003. May 6.
[16] Oxley TJ, Mocco J, Majidi S, et al. Large vessel stroke as a presenting feature of COVID-19 in the young. N Engl J Med 2020. https://doi.org/10.1056/NEJM.2009787.
[17] Lin L, Wang J, Ouyang X, et al. The immediate impact of the 2019 novel coronavirus (COVID-19) outbreak on subjective sleep status. Sleep Med 2020. https://doi.org/10.1016/j.sleep.2020.05.018.
[18] Zhang C, Yan L, Liu S, et al. Survey of insomnia and related social, psychological factors among medical staff involved with the 2019 novel coronavirus disease outbreak. Lancet Psychiatr 2020 (Preprint).
[19] Morin CM, Carrier J. The acute effects of the COVID-19 pandemic on insomnia and psychological symptoms. An Editorial Sleep Med 2020. https://doi.org/10.1016/j.sleep.2020.06.005.
[20] Patel AB, Verma A. COVID-19 and Angiotensin- Converting Enzyme inhibitors and Angiotensin Receptor Blockers. What is the evidence? JAMA 2020;323:1769–70.
[21] Mao L, Jin H, Wang M, et al. Neurological manifestations of hospitalized patients with coronavirus disease-2019 in Wuhan, China. JAMA Neurol 2020:1127. https://doi.org/10.1001/jamaneurol.2020 (Published online April 10, 2020).
[22] Li YC, Bai WZ, Hashikawa T. The neuroinvasive potential of SARS-COV2 may be at least partially responsible for the respiratory failure of COVID-19 patients. review. J Med Virol 2020:1–4. https://doi.org/10.1002/jmv.25728.

Sudhansu Chokroverty
Neuroscience Institute-JFK Medical Center Edison, NJ, USA
E-mail address: chokroverty123@gmail.com.

Available online 5 June 2020