SARS-CoV-2 and Brain

The second year of the COVID-19 (coronavirus disease) pandemic has seen the need to identify and assess the long-term consequences of a SARS-CoV-2 infection on an individual's overall wellbeing, including adequate cognitive functioning. 'Cognitive COVID' is an informal term coined to interchangeably refer to acute changes in cognition during COVID-19 and/or cognitive sequelae with various deficits following the infection. These may manifest as altered levels of consciousness, encephalopathy-like symptoms, delirium, and loss of various memory domains. Dysexecutive syndrome is a peculiar manifestation of 'Cognitive COVID' as well.

1. Introduction

Apart from major respiratory symptoms, there are reports of acute and post-recovery cognitive deficits occurring in COVID-19 patients [1]. Some authors [2] have also coined a more generic term 'infectious disease-associated encephalopathy' to encompass neurological manifestations of both the classical and novel infections. While it is assumed to have a separate pathophysiology than encephalopathy of a non-infectious origin [2], and although evidence of central nervous system (CNS) involvement exists for the 1918 H1N1 Influenza Virus and 2002 SARS-CoV [3], there is a lack of academic evidence necessary to evaluate the causality of cognitive impairments accurately. Nevertheless, several mechanisms have been presented to explain SARS-CoV-2's acute and 'sequelae' effects [4][5][6][7] on the brain. These include viral neurotropism, widespread systemic inflammation, and psychological burden of the pandemic across the world.

These sequelae consist of cognitive impairment after COVID-19 and have also been associated with the medical interventions, especially mechanical ventilation, provided to alleviate conditions of those with severe forms of the infection, which mainly manifested as acute respiratory distress syndrome (ARDS) [8]. Moreover, the immense psychosocial strain due to the prevailing conditions, rising mortality, and government-mandated distancing mechanisms such as lockdowns [9] may also lead to psychological and cognitive consequences in the long run [3].

2. History of Cognitive Impairment in Previous Major Coronavirus Outbreaks and Other Classical Infectious Diseases

Before SARS-CoV-2, two coronaviruses caused significant outbreaks—the Severe Acute Respiratory Syndrome caused by SARS-CoV in 2002 [10], and the Middle Eastern Respiratory Syndrome caused by MERS-CoV in 2012 [11].

Furthermore, the comparative pathophysiology of SARS and COVID-19 and a similar psychological strain caused by some of the disease processes and circumstances increase the likelihood that COVID-19 will present with cognitive impairments. SARS and COVID-19 both consist of extensive systemic inflammation, the level of which determines disease severity and outcomes [12]. Furthermore, a study on three MERS patients in Saudi Arabia revealed that they had altered levels of consciousness and confusion, which was correlated to new-onset changes on MRI imaging, indicating a neurological component of the viral infection [13].

This link, however, expands beyond just coronaviruses. For example, multiple studies conducted on viral infections involving the Human Immunodeficiency Virus (HIV) and Zika Virus (ZIKV) have also underscored a cognitive aspect to the disease presentation with attention, memory, and learning defects [14][15]. The Influenza viruses have also been reported to affect cognition and result in a cognitive decline. Neurological manifestations of Influenza (NMI) have been reported for both global and seasonal outbreaks of the virus and have ranged from seizures to encephalopathies [16].

3. Brief Review of Manifestation of Acute and Long-Term Cognitive Deficits

Acute decline in cognitive functions may result due to a combination of causes, including neurotropism of SARS-CoV-2 and sedation during mechanical ventilation. Encephalopathy is then cited as a general cause for the development of cognitive disturbances [17]. Early in the pandemic, a study involving 214 patients in Wuhan, China, noted CNS-related symptoms including dizziness, headache, and diminished consciousness in 24.8% of patients [18]. In April 2020, 'altered mental status' was listed as one of the 'clinical syndromes' associated with COVID-19 and defined as an 'acute alteration in personality, behavior, cognition, or consciousness' by a survey in the United Kingdom [19]. In the same survey, 31% of the patients recorded having an altered mental status following COVID-19, and nearly 5% of the total patients had dementia-like cognitive symptoms [19]. In addition, viral encephalitis has been identified in some COVID-19 patients, and it alone is possibly linked to the development of acute and lasting cognitive losses [3][20].

'Dysexecutive syndrome' is another peculiar concept that depicts cognitive defects in individuals, particularly of attention, control, and orientation loss [21]. Empirical evidence from a French study shows that loss of executive functions was reported in almost a quarter of COVID-19 patients presenting with ARDS [22].

Apart from lasting psychiatric conditions, cognitive impairments may follow a SARS-CoV-2 infection, causing impaired memory, confusion, and attention deficits in the long term [3][23]. A study in Zhejiang, China administered multiple tests evaluating attention, memory, executive function, and information processing, checking for cognitive function of recovered COVID-19 patients against a control group, and finding the sustained attention domain significantly lesser in COVID-19 survivors [24].

Lu et al. [25] recorded data of 60 patients during acute SARS-CoV-2 infection and at a 3-month follow-up visit. The proportion of patients with memory loss more than doubled from 13.3% during the acute disease to 28.3% at the follow-up [25], demonstrating the long-term impact of COVID-19 on an individual's cognition.

4. Causality

4.1. Neurotropism and the ACE2 Receptor

While still unclear, it is hypothesized that SARS-CoV-2, similarly to other coronaviruses, can infect and survive in nervous tissue [26][27]. Although rare, evidence of SARS-CoV-2's presence in cerebrospinal fluid (CSF) [20][28], as with other viruses [29], is available. There are numerous suggested pathways by which such neurotropism occurs. However, the exact mechanism is still uncertain. Retrograde neuronal access via peripheral nerves, hematogenous spread via directly infecting endothelial cells, and infiltration of infected cells are three main explanations [4][30][31][32] behind how respiratory viruses (such as SARS-CoV-2) enter the CNS.

Olfactory invasion: There is emerging evidence of SARS-CoV-2 affecting the olfactory and gustatory sensations, producing well-known symptoms of 'loss of taste and smell' in infected individuals [33][34][35]. With time, evidence has surfaced supporting the pathobiology of olfactory and gustatory dysfunction because of a direct invasion of the mucosal epithelium and olfactory bulb [36]. The invasion can potentially be attributed to their expression of the ACE2 surface receptor and Transmembrane Protease Serine 2 (TMPRSS2), cleaving the spike protein of SARS-CoV-2 and facilitating the fusion of SARS-CoV-2 with cellular membranes [37][38].

Hematogenous spread: Some authors [5] claim hematogenous spread via the cerebral vasculature plays a more critical role in direct brain entry and damage-causing cognitive deficits in COVID-19. Evidence of SARS-CoV-2's presence in blood samples of some confirmed COVID-19 patients exists. As many as 41% [39] of the samples showed viremia [32], showcasing the ability of the virus to easily reach the brain once the blood-brain barrier (BBB) is damaged. The distribution of SARS-CoV-2's functional (ACE2) receptor is widespread in endothelial cells and pericytes throughout the body [40]. Analysis of available genomic databases confirms noteworthy expression of the receptor in neuronal and glial tissues of the CNS [40]. Consequently, the nervous tissue is potentially vulnerable if the virus comes in direct contact and interacts with the ACE2 receptors. In addition, SARS-CoV-2's potential neurotropic properties may allow it to assume latency inside neuronal tissue of patients even after recovery from COVID-19, putting them at greater risk of long-term or delayed cognitive deficits and neurological symptoms [3].

Infiltration of infected cells: A 2005 study aimed at SARS-CoV found a sizeable proportion of immune cells (29.7% of monocytes and 51.5% of lymphocytes) in 6 out of 22 patients to contain viral particles [41], signaling their potential as a reservoir for the virus. If immune cells were to infiltrate the neuronal space by crossing the BBB, this would allow the viral particles in them to cause direct brain damage by binding to ACE2 receptors on neuronal and glial cells [4]. However,

whether these findings can be accurately extrapolated to SARS-CoV-2 remains yet to be ascertained. In addition, autopsies and studies conducted on samples obtained from infected individuals have been inconclusive about direct immune cell infiltration during COVID-19 [42].

4.2. Non-Specific Systemic Inflammation, Multisystem Inflammatory Syndrome (MIS), and ARDS

Widespread systemic inflammation: A significant increase in inflammatory cytokines plays a role in SARS symptoms, with inflammation persisting even after the viral clearance, and a similar ramped up an innate immune response in the form of 'cytokine storm' is behind COVID-19 as well [12][24][43]. Highly circulating amounts of Interleukins and other mediators (including IL-6, IL-1β, and TNF, and others) resulting in a pro-inflammatory status are commonly found in COVID-19 patients [44][45]. This amplified immune response may cause increased vascular permeability and vasculopathy arising from disseminated intravascular coagulation (DIC). Subsequently, the BBB is compromised, allowing cytokines to activate a microglial inflammatory response [46].

Multisystem Inflammatory Syndrome (MIS): Demographically, COVID-19 has been shown to cause more severe disease in adults, but increasing reports of COVID-associated Multisystem Inflammatory Syndrome (MIS) have surfaced [47][48][49]. While more prevalent in children, as MIS in children (MIS-C), it can potentially occur in adults as well (MIS-A). A meta-analysis comparing MIS-C's clinical course to COVID-19 revealed how it can potentially lead to multi-organ failure [50]. MIS-C was also shown to have a relatively higher incidence of neurological manifestations compared to acute COVID-19 [50]. As a distinct manifestation of a SARS-CoV-2 infection even in adults [51], with a high risk of neurological symptoms, MIS warrants discussion as a potential causal factor in the development of Cognitive COVID. MIS-C is considered to cause a hyperinflammatory shock and resembles Kawasaki Disease (KD) [52] or Toxic Shock Syndrome (TSS) [53]. Several cases with serologic evidence of a SARS-CoV-2 infection reported symptoms of MIS-C such as shock, cardiac symptoms, gastrointestinal complains, and elevated markers of inflammation, particularly after it was recognized by the Centers for Disease Control and Prevention (CDC) in May 2020 [53]. The pathophysiology of MIS-C during and after a SARS-CoV-2 infection is largely unknown [53]. Generally, MIS-C is believed to cause a dysregulated immune response possibly by viral mimicry of the host and development of autoantibodies. This leads to widespread systemic inflammation that potentially has a damaging impact on multiple systems, including the neurological system [54][55][56].

Acute respiratory distress syndrome (ARDS), mechanical ventilation, and associated cognitive decline: Although the exact ratio of COVID-19 patients developing severe disease and requiring hospitalization or intensive care unit (ICU) admission varies extensively, there is undoubtedly a noticeable proportion that progresses to life-threatening conditions [57]. Preliminary studies from China investigating data of more than 70 thousand patients suggested that around 19% of patients with COVID-19 develop severe or critical disease, most likely necessitating hospitalization [58]. A survey of 17 studies examining statistics of hospitalized COVID-19 patients from different regions found that one-third of all hospitalized and three-quarters of all ICU-admitted patients develop ARDS [57]. Cognitive impairment following ARDS of variable etiology is widely reported and reviewed [59]. Although severe inflammation, hemodynamic instability, and hypoxia have been indicted, the exact mechanism causing it is unknown. However, a review of studies has shown that cognitive impairment post-ARDS has a high incidence and ranges from 70–100% at hospital discharge, to 46–80% at one year after discharge, to 20% at five years after discharge [59]. In addition, an observational study in France described several ICU-admitted COVID-19 patients with complaints of ARDS developing encephalopathy manifesting as confusion and agitation [22]. According to Tzotzos et al., of the COVID-19 ICU-admitted patients who develop ARDS, more than 80% must receive mechanical ventilation [57]. Mechanical ventilation, regardless of ARDS, is associated with cognitive decline and reduced quality of life in the long run [60]. Since mechanical ventilation inextricably leads to the administration of sedatives, it is essential to note delirium and other cognitive consequences that may accompany, both in the short and long term [61]. The likelihood of a systemic inflammation playing a significant role in the development of cognitive loss compared to direct viral damage is underscored by the sparse evidence of the virus being found in the CSF [12].

4.3. The Psychosocial Strain of the Pandemic and Associated Lockdowns

Psychological stressors: While countries battle their second or third waves, confinement due to lockdowns and the fear of one or one's loved ones contracting COVID-19 are just some of the reasons that continue to cause an unprecedented psychological burden on people across the world [9][62]. With psychological conditions such as anxiety and depression now being recorded globally, cognitive consequences can be reasonably expected as a unique symptomatic presentation [63].

Social isolation and government-mandated lockdowns: An article published in late 2020 had reviewed the available evidence and stipulated that social distancing/isolation and lack of human interaction may have a detrimental effect on a person's cognition [64]. Echoing these findings, a study conducted in Italy during May 2020 investigated the effects of

psychological stressors as a result of isolation in the form of national lockdown as a mitigation technique on the global cognitive function of the public [65]. Findings suggested cognitive function such as barring memory deteriorated during lockdowns. Furthermore, with a greater prevalence of anxiety, depression, and other mental health changes, a significant deleterious impact on cognitive function(s) was noted in those who had lesser social interactions [65].

5. COVID-19 Vaccination, Autoimmunity, and Cognitive Impairment

The vaccine roll-out for COVID-19 began recently, but nearly 3.57 billion doses have been administered worldwide already [66]. Various vaccines were approved by the World Health Organization (WHO) for emergency use but all of them fall under three major subtypes: messenger RNA (mRNA), viral vector, and inactivated whole-virus [67]. As the pace of vaccine administration increases, more data is surfacing regarding post-vaccination adverse events. Neurocognitive symptoms following vaccinations COVID-19 vaccinations are rare but emerging case reports require due attention to accurately evaluate the pathophysiology and risk-factors carefully and accurately.

An interesting case is of an adult, who recovered from COVID-19 6 weeks ago, developing MIS following a second dose of an inactivated virus vaccine [68]. Features of shock and cardiac dysfunction were present in the patient along with elevated inflammatory markers, indicating MIS. The authors postulate that the vaccine may have accentuated their body's immune response which was 'already primed' following SARS-CoV-2 infection and therefore led to an uninhibited inflammatory condition in the body [68].

Some authors have warned against the use of certain immunogenic proteins of SARS-CoV-2 in vaccines that are homologous to the human immune system [69]. With most of SARS-CoV-2's immunogenic epitopes matching human proteins, there is a reasonable risk that vaccines containing these epitopes will lead to autoimmunity [69]. Excessive inflammation, creation of autoantibodies, and a series of biochemical processes due to autoimmunity may lead to neuroinflammation, damage to neuronal integrity and cognitive impairment [70].

6. Way Forward

Moving forward, greater attention should be paid to cognitive impairment during and after COVID-19 and vaccination. With the emergence of new strains of COVID-19, such as the Delta and the Lambda variant [71], the variation in prevalence of cognitive manifestations of the viral infection needs to be ascertained. Therefore, it is imperative to collect empirical data from multiple demographics in order to attain uniform clinical and biochemical information regarding causality and risk-factors in developing cognitive impairments.

References

1. Jaywant, A.; Vanderlind, W.M.; Alexopoulos, G.S.; Fridman, C.B.; Perlis, R.H.; Gunning, F.M. Frequency and profile of objective cognitive deficits in hospitalized patients recovering from COVID-19. Neuropsychopharmacology 2021, 15, 1–6.

2. Barbosa-Silva, M.C.; Lima, M.N.; Battaglini, D.; Robba, C.; Pelosi, P.; Rocco, P.R.M.; Maron-Gutierrez, T. Infectious disease-associated encephalopathies. Crit. Care 2021, 25, 236.

3. Kumar, S.; Veldhuis, A.; Malhotra, T. Neuropsychiatric and cognitive sequelae of COVID-19. Front. Psychol. 2021, 12, 577529.

4. Iadecola, C.; Anrather, J.; Kamel, H. Effects of COVID-19 on the nervous system. Cell 2020, 183, 16–27.e1.

5. Miners, S.; Kehoe, P.G.; Love, S. Cognitive impact of COVID-19: Looking beyond the short term. Alzheimers Res. Ther. 2020, 12, 170.

6. Pereira, A. Long-term neurological threats of COVID-19: A call to update the thinking about the outcomes of the coronavirus pandemic. Front. Neurol. 2020, 11, 308.

7. Uversky, V.N.; Elrashdy, F.; Aljadawi, A.; Ali, S.M.; Khan, R.H.; Redwan, E.M. Severe acute respiratory syndrome coronavirus 2 infection reaches the human nervous system: How? J. Neurosci. Res. 2020, 99, 750–777.

8. Rabinovitz, B.; Jaywant, A.; Fridman, C.B. Neuropsychological functioning in severe acute respiratory disorders caused by the coronavirus: Implications for the current COVID-19 pandemic. Clin. Neuropsychol. 2020, 34, 1453–1479.

9. Dubey, S.; Biswas, P.; Ghosh, R.; Chatterjee, S.; Dubey, M.J.; Chatterjee, S.; Lahiri, D.; Lavie, C.J. Psychosocial impact of COVID-19. Diabetes Metab. Syndr. Clin. Res. Rev. 2020, 14, 779–788.

10. Ksiazek, T.G.; Erdman, D.; Goldsmith, C.S.; Zaki, S.R.; Peret, T.; Emery, S.; Tong, S.; Urbani, C.; Comer, J.A.; Lim, W.; et al. A novel coronavirus associated with severe acute respiratory syndrome. N. Engl. J. Med. 2003, 348, 1953–1966.

11. Al-Osail, A.M.; Al-Wazzah, M.J. The history and epidemiology of Middle East respiratory syndrome corona virus. Multidiscip. Respir. Med. 2017, 12, 20.

12. Heneka, M.T.; Golenbock, D.; Latz, E.; Morgan, D.; Brown, R. Immediate and long-term consequences of COVID-19 infections for the development of neurological disease. Alzheimers Res. Ther. 2020, 12, 69.

13. Arabi, Y.M.; Harthi, A.; Hussein, J.; Bouchama, A.; Johani, S.; Hajeer, A.H.; Saeed, B.T.; Wahbi, A.; Saedy, A.; Aldabbagh, T.; et al. Severe neurologic syndrome associated with Middle East respiratory syndrome corona virus (MERS-CoV). Infection 2015, 43, 495–501.

14. Kanmogne, G.D.; Fonsah, J.Y.; Umlauf, A.; Moul, J.; Doh, R.F.; Kengne, A.M.; Tang, B.; Tagny, C.T.; Nchindap, E.; Kenmogne, L.; et al. Attention/Working memory, learning and memory in adult cameroonians: Normative data, effects of HIV infection and viral genotype. J. Int. Neuropsychol. Soc. 2020, 26, 607–623.

15. Raper, J.; Kovacs-Balint, Z.; Mavigner, M.; Gumber, S.; Burke, M.W.; Habib, J.; Mattingly, C.; Fair, D.; Earl, E.; Feczko, E.; et al. Long-term alterations in brain and behavior after postnatal Zika virus infection in infant macaques. Nat. Commun. 2020, 11, 2534.

16. Ekstrand, J.J. Neurologic Complications of Influenza. Semin. Pediatr. Neurol. 2012, 19, 96–100.

17. Filatov, A.; Sharma, P.; Hindi, F.; Espinosa, P.S. Neurological complications of coronavirus disease (COVID-19): Encephalopathy. Cureus 2020, 12, e7352.

18. Mao, L.; Jin, H.; Wang, M.; Hu, Y.; Chen, S.; He, Q.; Chang, J.; Hong, C.; Zhou, Y.; Wang, D.; et al. Neurologic manifestations of hospitalized patients with coronavirus disease 2019 in Wuhan, China. JAMA Neurol. 2020, 77, 683.

19. Varatharaj, A.; Thomas, N.; Ellul, M.A.; Davies, N.W.S.; Pollak, T.A.; Tenorio, E.L.; Sultan, M.; Easton, A.; Breen, G.; Zandi, M.; et al. Neurological and neuropsychiatric complications of COVID-19 in 153 patients: A UK-wide surveillance study. Lancet Psychiatry 2020, 7, 875–882.

20. Moriguchi, T.; Harii, N.; Goto, J.; Harada, D.; Sugawara, H.; Takamino, J.; Ueno, M.; Sakata, H.; Kondo, K.; Myose, N.; et al. A first case of meningitis/encephalitis associated with SARS-Coronavirus-2. Int. J. Infect. Dis. 2020, 94, 55–58.

21. Ardila, A.; Lahiri, D. Executive dysfunction in COVID-19 patients. Diabetes Metab. Syndr. Clin. Res. Rev. 2020, 14, 1377–1378.

22. Helms, J.; Kremer, S.; Merdji, H.; Clere-Jehl, R.; Schenck, M.; Kummerlen, C.; Collange, O.; Boulay, C.; Fafi-Kremer, S.; Ohana, M.; et al. Neurologic Features in Severe SARS-CoV-2 Infection. N. Engl. J. Med. 2020, 382, 2268–2270.

23. Wang, F.; Kream, R.M.; Stefano, G.B. Long-term respiratory and neurological sequelae of COVID-19. Med. Sci. Monit. 2020, 26, e928996.

24. Zhou, H.; Lu, S.; Chen, J.; Wei, N.; Wang, D.; Lyu, H.; Shi, C.; Hu, S. The landscape of cognitive function in recovered COVID-19 patients. J. Psychiatr. Res. 2020, 129, 98–102.

25. Lu, Y.; Li, X.; Geng, D.; Mei, N.; Wu, P.-Y.; Huang, C.-C.; Jia, T.; Zhao, Y.; Wang, D.; Xiao, A.; et al. Cerebral micro-structural changes in COVID-19 patients–An MRI-based 3-month follow-up study. EClinicalMedicine 2020, 25, 100484.

26. Kwong, K.C.N.K.; Mehta, P.R.; Shukla, G.; Mehta, A.R. COVID-19, SARS and MERS: A neurological perspective. J. Clin. Neurosci. 2020, 77, 13–16.

27. Valiuddin, H.M.; Kalajdzic, A.; Rosati, J.; Boehm, K.; Hill, D. Update on neurological manifestations of SARS-CoV-2. West. J. Emerg. Med. 2020, 21, 45–51.

28. Lewis, A.; Frontera, J.; Placantonakis, D.G.; Lighter, J.; Galetta, S.; Balcer, L.; Melmed, K. Cerebrospinal fluid in COVID-19: A systematic review of the literature. J. Neurol. Sci. 2021, 421, 117316.

29. Bohmwald, K.; Gálvez, N.M.S.; Ríos, M.; Kalergis, A.M. Neurologic alterations due to respiratory virus infections. Front. Cell. Neurosci. 2018, 12, 386.

30. Desforges, M.; Le Coupanec, A.; Dubeau, P.; Bourgouin, A.; Lajoie, L.; Dube, M.; Talbot, P.J. Human coronaviruses and other respiratory viruses: Underestimated opportunistic pathogens of the central nervous system? Viruses 2019, 12, 14.

31. Wu, Y.; Xu, X.; Chen, Z.; Duan, J.; Hashimoto, K.; Yang, L.; Liu, C.; Yang, C. Nervous system involvement after infection with COVID-19 and other coronaviruses. Brain Behav. Immun. 2020, 87, 18–22.

32. Zhou, Z.; Kang, H.; Li, S.; Zhao, X. Understanding the neurotropic characteristics of SARS-CoV-2: From neurological manifestations of COVID-19 to potential neurotropic mechanisms. J. Neurol. 2020, 267, 2179–2184.

33. Hornuss, D.; Lange, B.; Schröter, N.; Rieg, S.; Kern, W.; Wagner, D. Anosmia in COVID-19 patients. Clin. Microbiol. Infect. 2020, 26, 1426–1427.

34. Dawson, P.; Rabold, E.M.; Laws, R.L.; Conners, E.E.; Gharpure, R.; Yin, S.; Buono, S.A.; Dasu, T.; Bhattacharyya, S.; Westergaard, R.P.; et al. Loss of taste and smell as distinguishing symptoms of coronavirus disease 2019. Clin. Infect. Dis. 2020, 72, 682–685.

35. Mullol, J.; Alobid, I.; Mariño-Sánchez, F.; Izquierdo-Domínguez, A.; Marin, C.; Klimek, L.; Wang, D.-Y.; Liu, Z. The loss of smell and taste in the COVID-19 outbreak: A tale of many countries. Curr. Allergy Asthma Rep. 2020, 20, 61.

36. Mehraeen, E.; Behnezhad, F.; Salehi, M.A.; Noori, T.; Harandi, H.; SeyedAlinaghi, S. Olfactory and gustatory dysfunctions due to the coronavirus disease (COVID-19): A review of current evidence. Eur. Arch. Oto-Rhino-Laryngol. 2020, 278, 307–312.

37. Brann, D.H.; Tsukahara, T.; Weinreb, C.; Lipovsek, M.; Berge, K.V.D.; Gong, B.; Chance, R.; Macaulay, I.C.; Chou, H.-J.; Fletcher, R.B.; et al. Non-neuronal expression of SARS-CoV-2 entry genes in the olfactory system suggests mechanisms underlying COVID-19-associated anosmia. Sci. Adv. 2020, 6, eabc5801.

38. Dong, M.; Zhang, J.; Ma, X.; Tan, J.; Chen, L.; Liu, S.; Xin, Y.; Zhuang, L. ACE2, TMPRSS2 distribution and extrapulmonary organ injury in patients with COVID-19. Biomed. Pharmacother. 2020, 131, 110678.

39. Zheng, S.; Fan, J.; Yu, F.; Feng, B.; Lou, B.; Zou, Q.; Xie, G.; Lin, S.; Wang, R.; Yang, X.; et al. Viral load dynamics and disease severity in patients infected with SARS-CoV-2 in Zhejiang province, China, January-March 2020: Retrospective cohort study. BMJ 2020, 369, m1443.

40. Baig, A.M.; Khaleeq, A.; Ali, U.; Syeda, H. Evidence of the COVID-19 virus targeting the CNS: Tissue distribution, host–virus interaction, and proposed neurotropic mechanisms. ACS Chem. Neurosci. 2020, 11, 995–998.

41. Gu, J.; Gong, E.; Zhang, B.; Zheng, J.; Gao, Z.; Zhong, Y.; Zou, W.; Zhan, J.; Wang, S.; Xie, Z.; et al. Multiple organ infection and the pathogenesis of SARS. J. Exp. Med. 2005, 202, 415–424.

42. Solomon, I.H.; Normandin, E.; Bhattacharyya, S.; Mukerji, S.S.; Keller, K.; Ali, A.S.; Adams, G.; Hornick, J.L.; Padera, R.F.; Sabeti, P. Neuropathological features of Covid-19. N. Engl. J. Med. 2020, 383, 989–992.

43. Hu, B.; Huang, S.; Yin, L. The cytokine storm and COVID-19. J. Med. Virol. 2020, 93, 250–256.

44. Wang, J.; Jiang, M.; Chen, X.; Montaner, L.J. Cytokine storm and leukocyte changes in mild versus severe SARS-CoV-2 infection: Review of 3939 COVID-19 patients in China and emerging pathogenesis and therapy concepts. J. Leukoc. Biol. 2020, 108, 17–41.

45. Anderberg, S.B.; Luther, T.; Berglund, M.; Larsson, R.; Rubertsson, S.; Lipcsey, M.; Larsson, A.; Frithiof, R.; Hultström, M. Increased levels of plasma cytokines and correlations to organ failure and 30-day mortality in critically ill Covid-19 patients. Cytokine 2021, 138, 155389.

46. Boldrini, M.; Canoll, P.D.; Klein, R.S. How COVID-19 affects the brain. JAMA Psychiatry 2021, 78, 682–683.

47. Leon, M.P.D.; Redzepi, A.; McGrath, E.; Abdel-Haq, N.; Shawaqfeh, A.; Sethuraman, U.; Tilford, B.; Chopra, T.; Arora, H.; Ang, J.; et al. COVID-19–Associated pediatric multisystem inflammatory syndrome. J. Pediatr. Infect. Dis. Soc. 2020, 9, 407–408.

48. Cheung, E.W.; Zachariah, P.; Gorelik, M.; Boneparth, A.; Kernie, S.; Orange, J.S.; Milner, J.D. Multisystem inflammatory syndrome related to COVID-19 in previously healthy children and adolescents in New York City. JAMA 2020, 324, 294–296.

49. Sadiq, M.; Aziz, O.A.; Kazmi, U.; Hyder, N.; Sarwar, M.; Sultana, N.; Bari, A.; Rashid, J. Multisystem inflammatory syndrome associated with COVID-19 in children in Pakistan. Lancet Child. Adolesc. Health 2020, 4, e36–e37.

50. Yasuhara, J.; Watanabe, K.; Takagi, H.; Sumitomo, N.; Kuno, T. COVID-19 and multisystem inflammatory syndrome in children: A systematic review and meta-analysis. Pediatr. Pulmonol. 2021, 56, 837–848.

51. Morris, S.B.; Schwartz, N.G.; Patel, P.; Abbo, L.; Beauchamps, L.; Balan, S.; Lee, E.H.; Paneth-Pollak, R.; Geevarughese, A.; Lash, M.K.; et al. Case series of multisystem inflammatory syndrome in adults associated with SARS-CoV-2 infection—United Kingdom and United States, March–August 2020. MMWR. Morb. Mortal. Wkly. Rep. 2020, 69, 1450–1456.

52. Ebina-Shibuya, R.; Namkoong, H.; Shibuya, Y.; Horita, N. Multisystem inflammatory syndrome in children (MIS-C) with COVID-19: Insights from simultaneous familial Kawasaki disease cases. Int. J. Infect. Dis. 2020, 97, 371–373.

53. Godfred-Cato, S.; Bryant, B.; Leung, J.; Oster, M.E.; Conklin, L.; Abrams, J.; Roguski, K.; Wallace, B.; Prezzato, E.; Koumans, E.H.; et al. COVID-19–Associated multisystem inflammatory syndrome in children—United States, March–July 2020. MMWR. Morb. Mortal. Wkly. Rep. 2020, 69, 1074–1080.

54. Diorio, C.; Henrickson, S.E.; Vella, L.A.; McNerney, K.O.; Chase, J.M.; Burudpakdee, C.; Lee, J.H.; Jasen, C.; Balamuth, F.; Barrett, D.M.; et al. Multisystem inflammatory syndrome in children and COVID-19 are distinct presentations of SARS–CoV-2. J. Clin. Investig. 2020, 130, 5967–5975.

55. Jiang, L.; Tang, K.; Levin, M.; Irfan, O.; Morris, S.K.; Wilson, K.; Klein, J.D.; A Bhutta, Z. COVID-19 and multisystem inflammatory syndrome in children and adolescents. Lancet Infect. Dis. 2020, 20, e276–e288.

56. Maltezou, H.; Pavli, A.; Tsakris, A. Post-COVID syndrome: An insight on its pathogenesis. Vaccines 2021, 9, 497.

57. Tzotzos, S.J.; Fischer, B.; Fischer, H.; Zeitlinger, M. Incidence of ARDS and outcomes in hospitalized patients with COVID-19: A global literature survey. Crit. Care 2020, 24, 516.

58. Wu, Z.; McGoogan, J.M. Characteristics of and important lessons from the Coronavirus disease 2019 (COVID-19) outbreak in China. JAMA 2020, 323, 1239.

59. Sasannejad, C.; Ely, E.W.; Lahiri, S. Long-term cognitive impairment after acute respiratory distress syndrome: A review of clinical impact and pathophysiological mechanisms. Crit. Care 2019, 23, 352.

60. Jackson, J.C.; Hart, R.P.; Gordon, S.M.; Shintani, A.; Truman, B.; May, L.; Ely, E.W. Six-month neuropsychological outcome of medical intensive care unit patients. Crit. Care Med. 2003, 31, 1226–1234.

61. Girard, T.D.; Thompson, J.L.; Pandharipande, P.; Brummel, N.E.; Jackson, J.C.; Patel, M.B.; Hughes, C.G.; Chandrasekhar, R.; Pun, B.T.; Boehm, L.M.; et al. Clinical phenotypes of delirium during critical illness and severity of subsequent long-term cognitive impairment: A prospective cohort study. Lancet Respir. Med. 2018, 6, 213–222.

62. Ammar, A.; Mueller, P.; Trabelsi, K.; Chtourou, H.; Boukhris, O.; Masmoudi, L.; Bouaziz, B.; Brach, M.; Schmicker, M.; Bentlage, E.; et al. Psychological consequences of COVID-19 home confinement: The ECLB-COVID19 multicenter study. PLoS ONE 2020, 15, e0240204.

63. Ritchie, K.; Chan, D.; Watermeyer, T. The cognitive consequences of the COVID-19 epidemic: Collateral damage? Brain Commun. 2020, 2, fcaa069.

64. Bzdok, D.; Dunbar, R.I. The neurobiology of social distance. Trends Cogn. Sci. 2020, 24, 717–733.

65. Fiorenzato, E.; Zabberoni, S.; Costa, A.; Cona, G. Cognitive and mental health changes and their vulnerability factors related to COVID-19 lockdown in Italy. PLoS ONE 2021, 16, e0246204.

66. Dong, E.; Du, H.; Gardner, L. An interactive web-based dashboard to track COVID-19 in real time. Lancet Infect. Dis. 2020, 20, 533–534.

67. Drugs and Lactation Database(LactMed); National Library of Medicine(US): Bethesda, MD, USA, 2006; COVID-19 Vaccines. Available online: https://www.ncbi.nlm.nih.gov/books/NBK565969/ (accessed on 19 July 2021).

68. Uwaydah, A.K.; Hassan, N.M.M.; Abu Ghoush, M.S.; Shahin, K.M.M. Adult multisystem inflammatory syndrome in a patient who recovered from COVID-19 postvaccination. BMJ Case Rep. 2021, 14, e242060.

69. Lyons-Weiler, J. Pathogenic priming likely contributes to serious and critical illness and mortality in COVID-19 via autoimmunity. J. Transl. Autoimmun. 2020, 3, 100051.

70. Terrando, N.; Pavlov, V.A. Editorial: Neuro-immune interactions in inflammation and autoimmunity. Front. Immunol. 2018, 9, 772.

71. Callaway, E. Delta coronavirus variant: Scientists brace for impact. Nat. Cell Biol. 2021, 595, 17–18.