

# Pathophysiology of Psychiatric Symptoms in COVID-19 and Biomarkers (IL-6, Platelets, Ferritin, Lymphopenia and Urea)

Marcos Altable<sup>1\*</sup>, Juan Moisés de la Serna<sup>2</sup>, Emilio Díaz<sup>3</sup> and Adnan Srifi Hasnaoui<sup>4</sup>

<sup>1</sup>Department of Neurology, Neuroceuta, Virgen de Africa Clinic, Ceuta, Spain; <sup>2</sup>Department of Education, International University of La Rioja (UNIR), Madrid, Spain; <sup>3</sup>Department of Neuropsychology, Neuroceuta, Ceuta, Spain; <sup>4</sup>Health Center of INGESA, Ceuta, Spain

Corresponding author:  
Marcos Altable, Department of  
Neurology, Neuroceuta, Virgen  
de Africa Clinic, Ceuta, Spain,  
Tel:0034645066044; E-mail:  
sciencetextinfo@gmail.com

## Abstract

Most of the studies on the COVID-19 pandemic produced by the SARS-CoV-2 reported neuropsychiatric symptoms only as part of the manifestations of the disease in its terminal phase. However, there are neuropsychiatric symptoms since the beginning of the disease. Several investigations have indicated a direct relationship between chronic diseases such as Human Immunodeficiency Virus (HIV), tuberculosis, SARS, MERS, Ebola and SARS 2003 with mental disorders such as depression. Neuropsychiatric disorders can occur due to different mechanisms, such as cerebral hypoxia, cytokine storm due to exaggerated immune response and encephalitis due to direct brain infection. Nervous system involvement leads to poor prognosis of COVID-19.

**Keywords:** COVID-19; Biomarkers; Psychiatric disorders

## Introduction

The Central Nervous System (CNS) is vulnerable to viruses. <sup>[1]</sup> Historically, past influenza pandemics have been associated with a post-infection increase in anxiety, insomnia, fatigue, depression, suicidality, and delirium. <sup>[2]</sup> Furthermore, there is some debate about whether the Spanish flu pandemic of 1918 was causally associated with encephalitis lethargica as a neurological consequence. <sup>[3]</sup> Other viruses end up reaching the brain, such as herpes virus, arbovirus, coronavirus, measles, and HIV, among others. It is though SARS CoV-2 is a neurotropic virus and leads to a neuroinvasion of CNS from peripheral nerves (olfactory, trigeminal) and then reaches the cardiorespiratory nucleus of the brainstem. <sup>[4]</sup>

Most of the studies on the COVID-19 pandemic produced by the SARS-CoV-2 coronavirus, report neuropsychiatric symptoms only as part of the manifestations of the disease in its terminal phase. However, even if the infection is mild, moderate or severe, there are neuropsychiatric symptoms since the beginning of the disease.

Already in the advanced stages of the Severe Acute Respiratory Syndrome (SARS), different neuropsychiatric manifestations have been reported as a form of clinical expression of the course of infection, which could be a direct output of cerebral hypoxia due to respiratory failure, viral brain tissue infection or encephalitis, immune system reaction or cytokine storm or a combination of all these factors. <sup>[5-9]</sup> Neuropsychiatric manifestations include anxiety symptoms, panic attacks, depression, mental confusion, acute confusional syndrome, psychomotor excitement, psychosis, and even suicidal tendencies. <sup>[5-9]</sup>

According to studies reviewed to date, neuropsychiatric symptoms can be divided into symptoms of the Central Nervous

System (CNS), such as headache, dizziness, vertigo, altered consciousness, confusion, ataxia, acute cerebrovascular disease and seizures; Peripheral Nervous System (PNS) symptoms, such as anosmia, dysgeusia, neuralgia, and diarrhoea; and psychiatric symptoms such as apathy, depression, anorexia, psychosis, acute confusional syndrome and agitation.

Several investigations have indicated a direct relationship between chronic diseases such as Human Immunodeficiency Virus (HIV), herpesvirus and tuberculosis, with psychiatric symptoms <sup>[10-14]</sup> in the general population. <sup>[15,16]</sup> Similarly, studies conducted during and after epidemics such as SARS 2003 and Ebola 2014 found a widespread behaviour induced by the hyperactive reaction among the general public. <sup>[17,18]</sup> In addition to this, various psychiatric disorders such as anxiety, depression, and Post Traumatic Stress Disorder (PTSD) were found mainly in survivors and healthcare workers. <sup>[19-21]</sup>

Previous studies have reported adverse psychological reactions to the 2003 SARS outbreak among healthcare workers. <sup>[22-25]</sup> Studies showed that these health workers feared contagion and infection from their family, friends and colleagues, <sup>[24]</sup> felt uncertainty and stigmatization WHO, Wu et al., reported aversion to work, and high levels of stress, anxiety and symptoms of depression, <sup>[23]</sup> that could have long-term psychological implications. Similar concerns are now emerging about mental health, psychological adjustment, and recovery for both the ill and the health workers who treat and care for

This is an open access article distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 3.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as the author is credited and the new creations are licensed under the identical terms.

**How to Cite this Article:** Altable M, et al. Pathophysiology of Psychiatric Symptoms in COVID-19 and Biomarkers (IL-6, Platelets, Ferritin, Lymphopenia and Urea). *Ann Med Health Sci Res.* 2021;11:1483-1487.

patients with COVID-19. Besides, as the WHO has highlighted in its state of mental health, stigmatization and the scapegoat of affected people, including health professionals, is very common during epidemics. [26,27] Unfortunately, this trend continues to prevail during the current COVID-19 outbreak, as many people of Asian origin, explicitly Chinese, are victims of xenophobia and social stigmatization, with high levels of threats online and during public interactions. [28]

Initially, the public emotional response to any pandemic is one of extreme fear and uncertainty that generally leads to negative social behaviours and can involve public mental health problems such as anxiety, insomnia, aggression, depression, frustration, and hysteria. [27] Compared to preceding studies related to SARS outbreaks, patients with COVID-19 (defined or suspected), and in quarantine, are more likely to suffer from loneliness, anger and frustration. [29] Similarly, another concern is that survivors and mental health professionals suffer from PTSD. A study conducted at a Beijing hospital, quarantined health workers who worked in high-risk settings or had a family member with SARS, reported a significantly higher level of posttraumatic stress symptoms than those without similar experiences. [25,30,31] Similarly, medical professionals who dealt with SARS patients or worked during the SARS outbreak also reported fear, anxiety, depression, and frustration. [5,25] In comparison, health professionals working in COVID-19 quarantined units, lacking adequate protective measures and suffering the death of other physicians, may develop severe symptoms of PTSD. For this reason, mental health professionals must apply therapies such as the stress adaptation model to reduce the level of high stress in this population. [32]

Any situation of uncertainty can lead to alarmist behaviour, and with the influence of COVID-19, confinement, and the absence of adequate treatment for infectious disease, this situation has run the masses to moments of panic and anxiety. [33] Similarly, the obsession with contamination, which is persistent, for cleaning and the constant need for washing or sterilization is generally classified under obsessive-compulsive disorder. [34] Moreover, in the event of a pandemic caused by an infectious virus, this disorder can contribute to panic, resulting in disruption and impairment of the necessary daily activities of people. Mental health professionals and clinical psychologists must be alert to these impending problems and try to resolve them with the utmost care.

### Pathophysiology

In many patients infected with SARS-CoV-2 and, even more, in those who develop moderate to severe respiratory failure, neuropsychiatric disorders can occur due to different mechanisms that can act concomitantly, such as cerebral hypoxia due to respiratory failure (mental confusion), cytokine storm due to exaggerated immune response (apathy, anorexia and muscular pain) and encephalitis due to direct brain infection (agitation and psychosis). [7-9,20,35,36]

The Angiotensin 2-Converting Enzyme (ACE2) has been identified as the functional receptor for SARS-CoV-2, present in multiple human organs, including nervous and the musculoskeletal systems. The expression and distribution of

ACE2 explain why SARS-CoV-2 can produce neuropsychiatric symptoms through direct and indirect mechanisms. [4] Coronavirus encephalitis has also been confirmed, as in SARS-CoV and MERS-CoV. The researchers detected SARS-CoV nucleic acid in the cerebrospinal fluid of these patients and also brain tissue from the autopsies. [7-9,22,23,25]

Another mechanism involved in many genetically predisposed healthy patients and those with certain diseases such as Down's Syndrome, [37] is the cytokine storm generated by the interaction of the immune system with the virus, which, in addition to the systemic repercussion, primarily affects the nervous system. Cytokine storm resembles Macrophage Activation Syndrome (MAS), a severe condition that presents with hypercytokinemia, fever, cytopenia and hyperferritinemia; pulmonary involvement (including ARDS) and is associated with the severity of COVID-19 disease. It is characterized by an increase in Interleukin (IL) -2, IL-7, granulocyte colony-stimulating factor, interferon-inducible protein 10- $\gamma$ , monocyte chemo attractant protein 1, macrophage inflammatory protein 1- $\alpha$  and tumour necrosis factor- $\alpha$ . [7-9,38]

Brain cytokines produce behavioural changes (sickness behaviour) during the course of an illness or infection, manifesting depressive symptoms such as emotional hyperresponsiveness, apathetic syndrome, anhedonia, hyporexia, weight loss, hypersomnia, alteration of the circadian rhythm, fatigue and chronic pain, psychomotor inhibition, demotivation, disinterest and alteration of higher mental functions, etc. [39-42] Furthermore, it has been described a high level of these cytokines in blood and the prefrontal cortex of teenage suicide victims. [43] Recently, it is suggested that the COVID-19 survivors especially individuals who had severe COVID-19 are at increased suicide risk. Suicidality among individuals who had COVID-19 may be related to both psychological and neurobiological factors. [44] It would appear that during acute coronavirus infection, immune hyper reactivity generates this behaviour syndrome with such variable neuropsychiatric symptoms. This is important since in terms of COVID-19 infection, beyond the typical symptoms of fever, cough and dyspnea, the neuropsychiatric manifestations are added, which would be responsible for the symptoms of apathy, anorexia and muscular pain. These symptoms can go as far as the mental confusion, agitation, and psychosis that many patients may manifest even in initial stages, together with characteristic laboratory findings and pulmonary abnormalities. [45]

### Neurological Complications

Today we know from a recent study [36] that since the beginning of the disease, 66% of hospitalized patients started with the most common symptoms like fever, dry cough, and dyspnea, but 34% started with neurological symptoms such as dizziness (16%), headache (13%), dysgeusia (6%), and anosmia (5%). Furthermore, 40% of the total studied patients were severe, and 60% were non-severe, and within severe cases, 50% had neuropsychiatric symptoms. Within the non-severe group, 30% of cases presented neuropsychiatric symptoms. While within the group of severe cases with neuropsychiatric symptoms, these were due to stroke (5.7%), ischemic/haemorrhagic (4 to 1), altered consciousness (14.8%), and rhabdomyolysis (19.3%). Severe patients had a higher inflammatory response, including

leucocytosis, neutrophilia, lymphopenia, increased C-Reactive Protein (CRP) and higher D-dimer than non-severe cases, with D-dimer being an indicator of consumption coagulation pattern. Furthermore, severe patients had multiple organ involvement, such as liver failure (increased LDH, TGO, TGP), kidney failure (increased urea and creatinine), and rhabdomyolysis (increased CPK levels).<sup>[36]</sup> In the laboratory findings of patients with more severe neuropsychiatric symptoms, lymphopenia, platelet count, and increased urea were found. For the non-severe subgroup, there were no significant differences in the laboratory findings of patients with and without neuropsychiatric symptoms. Patients with rhabdomyolysis had leucocytosis, lymphopenia, and increased CRP and D-dimer. Abnormalities were a manifestation of an increased inflammatory response and impaired coagulation function. Additionally, it was observed that patients with rhabdomyolysis had multiple organ damage, including liver failure and kidney failure. For the severe group, patients with rhabdomyolysis had an increased inflammatory response (lymphopenia and increased CRP), liver failure, kidney, and rhabdomyolysis with increased CPK.<sup>[36]</sup>

Likewise, 33% of the total of patients, severe and non-severe, had diverse neuropsychiatric manifestations. The severe patients were older ( $58 \pm 10$  years). The most frequent comorbidity in these cases was hypertension and, less frequently, they presented typical symptoms such as fever, cough and dyspnea. Furthermore, they were more likely to develop neuropsychiatric symptoms, especially mental confusion, agitation, psychosis, and acute cerebrovascular disease.<sup>[36,46]</sup>

About 30% of the total of hospitalized patients had neuropsychiatric manifestations from the beginning of the infection, and the most severe or terminal patients probably develop neuropsychiatric symptoms in 45% as a manifestation of metabolic alteration of brain injury.<sup>[36]</sup>

The interpretation of the data now is that, compared to non-severe patients with COVID-19, severe patients very frequently presented as predictors of mortality, elevated ferritin and IL-6 as biomarkers of viral inflammation and neuropsychiatric symptoms as alteration of consciousness, mental confusion, agitation, cerebrovascular disease, encephalitis, and rhabdomyolysis.

A newly published study classifies neurological damage in patients with COVID-19 in three stages. On Stage I, the virus damage is limited to epithelial cells of nose and mouth, and the main symptoms include transient loss of smell and taste. Subsequently, on Stage II, the virus triggers a wave of inflammation, called a cytokine storm, which begins in the lungs and travels in the blood vessels throughout all body organs. This cytokine storm leads to the formation of blood clots which cause cerebrovascular disease.<sup>[46]</sup> Finally, on Stage III an explosive level of cytokine storm damages the Blood-Brain Barrier (BBB), and as a result, blood content, inflammatory markers, and virus particles invade the brain and patients develop seizures, confusion, coma, or encephalopathy.<sup>[47]</sup>

With all of the above, the new clinical information on COVID-19 would help to take into account the participation of neuropsychiatric manifestations, especially in patients with severe COVID-19, due to the rapid clinical deterioration

or worsening that could be more related frequently with the appearance of mental confusion, confusional syndrome, agitation and strokes. Therefore, increasing the mortality rate. Likewise, during the epidemic period of COVID-19, when treating patients with neuropsychiatric manifestations, SARS-CoV-2 infection should be considered a first-line differential diagnosis to avoid late or misdiagnosis to prevent transmission.<sup>[36]</sup>

Neuropsychiatric symptoms were the main form of manifestation of altered brain metabolism or neurological injury in reported COVID-19 patients. The pathophysiological mechanism could be the invasion of the Central Nervous System (CNS) by SARS-CoV-2, similar to the SARS and MERS viruses. Like other respiratory viruses, SARS-CoV-2 can enter the CNS *via* the hematogenous or retrograde neuronal pathway (since many patients presented anosmia or dysgeusia in initial stages).<sup>[4]</sup> Lymphopenia has also been detected in patients with neuropsychiatric symptoms. This phenomenon may indicate immunosuppression in COVID-19 patients with neuropsychiatric symptoms, especially in severe subgroup.

On the other hand, severe cases have also been found to have high D-dimer suggestive of a hypercoagulable state. This fact may be the reason why seriously ill patients are more likely to develop cerebrovascular disease.<sup>[46]</sup>

In summary, SARS-CoV-2 can infect the nervous system, the skeletal muscle and the respiratory tract. In those with severe infection, neuropsychiatric involvement is more likely, including altered consciousness, mental confusion, agitation, acute cerebrovascular disease, and rhabdomyolysis. Nervous system involvement leads to poor prognosis due to greater hemodynamic instability, worsening clinical conditions and increased mortality.

## Conclusion

Neuropsychiatric disorders can occur due to different mechanisms, such as cerebral hypoxia, cytokine storm due to exaggerated immune response and encephalitis due to direct brain infection. Nervous system involvement leads to poor prognosis of COVID-19.

## Conflict of Interest

Marcos Altable and Juan Moisés de la Serna have no conflicts of interest to disclose regarding the manuscript. The authors declare that the manuscript was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest. This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

## References

1. Xia H, Lazartigues E. Angiotensin-converting enzyme 2: Central regulator for cardiovascular function. *Curr Hypertens Rep.* 2010;12:170-175.
2. Honigsbaum M. "An inexpressible dread": Psychoses of influenza at fin-de-siècle. *Lancet* 2013;381:988-989.
3. Hoffman LA, Vilensky JA. Encephalitis lethargica: 100

- years after the epidemic. *Brain* 2017;140:2246-2251.
4. Altable M, de la Serna JM. 2020a. Neuropathogenesis in COVID-19. *J Neuropathol Exp Neurol.* 2020a;79:1247-1249.
  5. Liu TB, Chen XY, Miao GD, Zhang L, Zhang Q, Cheung T. Recommendations on diagnostic criteria and prevention of SARS-related mental disorders. *J Clin Psychol Med.* 2003;13:188-191.
  6. Ibrahim E, Ibrahim NE. Review of published systematic reviews and meta-analyses on COVID-19. *Med Rxiv.* 2020.
  7. Jain V, Jain M, Saluja SS, Saluja MS, Chaturvedi V, Rahman A, Mukim M. Coronavirus Disease: A Review. *ISET - Int J Innov Sci Eng Technol.* 2020;7:2348-7689.
  8. Katta M, Rapaka S, Adireddi R, Emandi JR. A Preliminary Review on Novel Coronavirus Disease: COVID-19. *Coronaviruses* 01. 2020.
  9. Tejaswi JKD. Overview on COVID 19: A Review. *World J Pharm Med Res.* 2020;6:151-153.
  10. Gale SD, Berrett AN, Erickson LD, Brown BL, Hedges DW. Association between virus exposure and depression in US adults. *Psychiatry Res.* 2018;261:73-79.
  11. Lectures. *Acta Neuropsychiatr.* 2008;20:1-50.
  12. Mason BW, Lyons RA. Acute psychological effects of suspected bioterrorism. *J Epidemiol Community Health.*2003;57:353-354.
  13. Timmerman L, Van Zonneveld T, Van Den Heuvel OA. Neuropsychiatric aspects of HIV infection. *Acta Neuropsychiatr.* 1998;10:90-92.
  14. Vollmer-Conna U, Chen M, Lloyd A, Donovan B. Neuropsychiatric symptoms and immune activation in patients with genital herpes. *Acta Neuropsychiatr.* 2008;20:145-151.
  15. Kuan V, Denaxas S, Gonzalez-Izquierdo A, Direk K, Bhatti O, Husain S, et al. A chronological map of 308 physical and mental health conditions from 4 million individuals in the English National Health Service. *Lancet Digit. Heal.* 2019;1:e63-e77.
  16. Van Den Heuvel L, Chishinga N, Kinyanda E, Weiss H, Patel V, Ayles H, et al. Frequency and correlates of anxiety and mood disorders among TB- and HIV-infected Zambians. *AIDS Care-Psychol. Socio-Medical Asp. AIDS/ HIV* 2013;25:1527-1535.
  17. Person B, Sy F, Holton K, Govert B, Liang A, Garza B, et al. Fear and stigma: The epidemic within the SARS outbreak. *Emerg Infect Dis.* 2004.
  18. Shultz JM, Cooper JL, Baingana F, Oquendo MA, Espinel Z, Althouse BM, et al. The role of fear-related behaviors in the 2013–2016 West Africa ebola virus disease outbreak. *Curr Psychiatry Rep.* 2016.
  19. Blakey SM, Kirby AC, McClure KE, Elbogen EB, Beckham JC, Watkins LL, et al. Posttraumatic safety behaviors: Characteristics and associations with symptom severity in two samples. *Traumatology.*2019.
  20. Gardner PJ, Moallem P. Psychological impact on SARS survivors: Critical review of the english language literature. *Can Psychol.* 2015.
  21. Mak IWC, Chu CM, Pan PC, Yiu MGC, Chan VL. Long-term psychiatric morbidities among SARS survivors. *Gen Hosp Psychiatry.*2009;31:318-326.
  22. Arabi YM, Balkhy HH, Hayden FG, Bouchama A, Luke T, Baillie JK, et al. Middle east respiratory syndrome. *N Engl J Med.* 2017;376:584-594.
  23. Hamming I, Timens W, Bulthuis MLC, Lely AT, Navis GJ, van Goor H. Tissue distribution of ACE2 protein, the functional receptor for SARS coronavirus. A first step in understanding SARS pathogenesis. *J Pathol.* 2004;203:631-637.
  24. WHO. Middle East Respiratory Syndrome Coronavirus (MERS-CoV). *Web World Heal Organ.* 2020a.
  25. Wu P, Fang Y, Guan Z, Fan B, Kong J, Yao Z, et al. The psychological impact of the SARS epidemic on hospital employees in China: Exposure, risk perception, and altruistic acceptance of risk. *Can J Psychiatry.*2009;54:302-311.
  26. Rubin GJ, Wessely S. The psychological effects of quarantining a city. *BMJ.* 2020.
  27. Shigemura J, Ursano RJ, Morganstein JC, Kurosawa M, Benedek DM. Public responses to the novel 2019 coronavirus (2019-nCoV) in Japan: Mental health consequences and target populations. *Psychiatry ClinNeurosci.* 2020.
  28. WHO. Mental health and psychosocial considerations during the COVID-19 outbreak. *Web World Heal Organ.* 2020b.
  29. Xiang YT, Yang Y, Li W, Zhang L, Zhang Q, Cheung T, et al. Timely mental health care for the 2019 novel coronavirus outbreak is urgently needed. *The Lancet Psychiatry.*
  30. Kaiser F. Framing risk, reducing panic during virus outbreak: *Asia Times.*2020.
  31. Yi Y, Lagniton PNP, Ye S, Li E, Xu RH. COVID-19: What has been learned and to be learned about the novel coronavirus disease. *Int J Biol Sci.* 2020;16:1753-1766.
  32. Folkman S, Greer S. Promoting Psychological Well-Being in the Face of Serious Illness: When Theory, Research and Practice Inform Each Other. *Psycho Oncology.* 2000;9.
  33. Soofi M, Najafi F, Karami-Matin B. Using insights from behavioral economics to mitigate the spread of COVID-19. *Appl Health Econ Health Policy.*2020;18:345-350.
  34. Williams MT, Mugno B, Franklin M, Faber S. Symptom dimensions in obsessive-compulsive disorder: Phenomenology and treatment outcomes with exposure and ritual prevention. *Psychopathology* 2013;46:365-376.
  35. Ahmed SF, Quadeer AA, McKay MR. Preliminary identification of potential vaccine targets for the COVID-19

- Coronavirus (SARS-CoV-2) based on SARS-CoV immunological studies. *Viruses* 2020;12:254.
36. Mao L, Jin H, Wang M, Hu Y, Chen S, He Q, et al. Neurologic manifestations of hospitalized patients with coronavirus disease 2019 in Wuhan, China. *JAMA Neurol.* 2020;77:683-690.
37. Altable M, de la Serna JM. Down's syndrome and COVID-19: risk or protection factor against infection? A molecular and genetic approach. *Neurol Sci.* 2020b;1-7.
38. Mehta P, McAuley DF, Brown M, Sanchez E, Tattersall RS, Manson JJ. COVID-19: consider cytokine storm syndromes and immunosuppression. *Lancet* 2020;395:1033-1034.
39. Dantzer R, O'Connor JC, Freund GG, Johnson RW, Kelley KW. From inflammation to sickness and depression: When the immune system subjugates the brain. *Nat Rev Neurosci.* 2008;9:46-56.
40. Debnath M, Berk M, Maes M. Changing dynamics of psychoneuroimmunology during COVID-19 pandemic. *Brain Behav Immun Heal.* 2020;5:100096.
41. Miller AH. Mechanisms of cytokine-induced behavioral changes: Psychoneuroimmunology at the translational interface. *Brain Behav Immun.* 2009;23:149-158.
42. Raison CL, Capuron L, Miller AH. Cytokines sing the blues: Inflammation and the pathogenesis of depression. *Trends Immunol.* 2006;27:24-31.
43. Pandey GN, Rizavi HS, Ren X, Fareed J, Hoppensteadt DA, Roberts RC, et al. Pro inflammatory cytokines in the prefrontal cortex of teenage suicide victims. *J Psychiatr Res.* 2012;46:57-63.
44. Sher L. Are COVID-19 survivors at increased risk for suicide? *Acta Neuropsychiatr.* 2020.
45. Guan W, Ni Z, Hu Y, Liang W, Ou C, He J, et al. Clinical characteristics of 2019 novel coronavirus infection in China. *N Engl J Med.* 2020.
46. Altable M, de la Serna JM. Cerebrovascular Disease in COVID-19: Is There a Higher Risk of Stroke? *Brain Behav Immun Heal.* 2020c;6:100092.
47. Fotuhi M, Mian A, Meysami S, Raji CA. Neurobiology of COVID-19. *J Alzheimer's Dis.* 2020;1-17.