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Could COVID-19 Cause Lasting Neuropsychological Effects?

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Abstract

Whereas COVID-19 is more usually thought to cause potentially irreversible lung damage and associated respiratory problems, in actuality, the damage may extend far beyond the lungs and reach into the brain potentially causing future neuropsychological problems. Like other pathogens already observed in the brain, the SARS CoV-2 virus may also unsurprisingly be detected there. In addition to other communication pathways, the link of the brain to various pathogens is mediated by the loss of impermeability, disruption or even breakdown of the brain protective barriers, particularly the blood-brain barrier. In this regard, the connection noted between the 1918 'Spanish' flu epidemic and Parkinson's disease is not unique in the relation between viruses and neurological problems. That relation also includes, for example, the connection with measles, HIV, memory deficits, multiple sclerosis, the connection between human herpes viruses-6 and -7 infections and Alzheimer's disease, and others. The implications for several neuropsychological disorders are discussed (such as psychiatric and neuropsychiatric disorders, and cognitive decline and motor impairment).

Abbreviations: AA: Alzheimer's Association; ACE: Angiotensin converting enzyme; AD: Alzheimer's disease; ARDS: Acute respiratory distress syndrome; BBB: Blood-brain barrier; CMV: Cytomegalovirus; CNS: Central nervous system; CoV: Coronary virus; COVID: Coronavirus ID; EBV: Epstein-Barr virus; GBA: Gut-brain axis; HHV: Human herpes viruses; HIV: Human immunodeficiency virus; HPAA: Hypothalamic-pituitary-adrenal axis; HS: herpes simplex; HZ: Herpes zoster; IBD: Inflammatory bowel disease; IBS: Inflammatory bowel syndrome; ICU: Intensive care unit; IL6: Interleukin-6; MS: Multiple sclerosis; NDD: Neurodegenerative disorders; NPDD: Neuropsychodegenerative diseases; PD: Parkinson's disease; PNS: Peripheral nervous system; PTSD: Post-traumatic stress disorder; SARS: Severe acute respiratory syndrome; WHO: World Health Organization; WNV: West Nile virus.

As of 21 May 2021, the World Health Organization (WHO) reported 165,069,258 confirmed COVID-19 cases, 3,422,907 deaths from it, and 1,422,282,170 administered vaccine doses (corresponding respectively to ~ 2.1%, ~ 0.04%, and ~ 18% of the world population) - all numbers increasing daily. (The pharmaceutical company Pfizer has further pledged to deliver 1 billion additional vaccines to poor countries that could not vaccinate their populations either because they could not afford or/and get the vaccines.) The lingering chronic sequelae of the pandemic will only add to our already heavy global public health burden. However important, I will not consider here the wider societal impact of the pandemic (political, economical, social, familial, and personal) in the immediate and longer term.

Introduction

As the COVID-19 pandemic is abating in several world regions, we are learning more about its short- and long-term effects on the body.

While it starts with basic flu symptoms, it could eventually affect each organ and system. During infection, the virus binds to a receptor located in the membrane of the host's cell (an angiotensin-converting enzyme type 2, ACE-2). It can then enter the cell either through endocytosis or fuse its membrane to the cell's membrane. It then releases its genome and protein content directly into the cell's cytoplasm. While present in various organs and tissues, the distribution of ACE-2 is not uniform so that some organs might be more prone to infection than others. This can explain the spread of the virus beyond the respiratory tract and the damage to certain organs found in the severe forms of the disease.

Once it enters the upper respiratory tract (nose, sinus cavity, and throat), if not subdued by the body's immune system, the virus travels to the lower respiratory system attacking the cells that line the lungs eventually leading to pneumonia (Fymat, 2018b, c). In acute respiratory distress syndrome (ARDS), the pneumonia worsens quickly and the body's response can damage the lungs even more to the point when blood oxygen levels get dangerously low. An overblown immune system may cause a cytokine storm causing the immune cells to attack healthy tissues, leading to low blood pressure, blood vessel damage (by attacking the lining cells and causing blood clots that may lead to a stroke or pulmonary embolism), and organ damage (liver tissues, eye problems such as conjunctivitis, kidney damage) or even failure. A number of heart problems (acute cardiac injury, arrhythmia, cardiac myopathy, shock) have also been observed in some (Hess *et al*., 2020).

Of importance here are other problems that may affect the central nervous system (CNS) (inflammation) and the brain (swelling, seizures, loss of sense of smell, loss of consciousness, and stroke) that could have a lasting effect on the brain (Asadi-Pooya and Simani, 2020; Jang *et al*., 2009; Koralnik *et al*. 2020; Paniz-Mondolfi *et al*., 2020; Saleki *et al*., 2020; Wang *et al*., 2020; Wu *et al*., 2020 a,b) and the later-life cognitive decline associated with Alzheimer's, other dementia-types, and other neurodegenerative disorders (Naughton *et al*., 2020; Ogata *et al*., 1997). In this regard, the Alzheimer's Association recently sponsored an international Consortium with charge to prospectively study some of the above effects, the associated risks, and the short-and long-term consequences on the central nervous system (CNS), including Alzheimer's disease (AD) and other dementias. More than 30 countries are participants of the Consortium. It will analyze more than 22 million COVID-19 cases worldwide (de Erausquin *et al*., 2021). Because of its enrollment and design (follow-ups at 6, 9, and 18 months), the results of this prospective study will only be known in approximately two years or more. The anticipated results from this study will be highly important in better understanding the short- and long-term effects of SARS CoV-2 on brain function. To be clear, such results will not generally be unexpected but will provide a more accurate assessment of the nature and extent of the potential neuropsychodegenerative effects of SARS CoV-2. Other contributing factors, unfortunately not in the charter of the Consortium, would be the deleterious effects on the brain-in-the-gut and their modulations of the former effects.

Rapid viral replication in the host cell causes massive inflammatory cell death (or pyroptosis) in the lung tissues, leading to the decreased respiratory capacity observed in severe SARS CoV-2 infections. Inflammation is an essential part of our immune defenses to control infection. However, in COVID-19, it is somewhat different from the inflammation caused by other respiratory infections. Pneumonia is a hallmark of severe COVID-19 and the most life-threatening complication. Understanding the underlying inflammation mechanism and how it contributes to major psychiatric disorders, will be important in leading to a therapy and preventing not only persistent lung injury but also major psychiatric disorders and their sequelae. Equally important but separate issues not considered here will be the disproportionate effects on certain groups of individuals and societies, and the immediate and longer term political, economical, financial, social, and personal effects.

Observed Neuropsychological Symptoms Caused by COVID-19

While some people with the viral COVID-19 illness do not experience any symptoms, others have symptoms that may range from mild to severe including: dry cough, fever, and difficulty breathing. A sizable portion of these individuals (say ~15%-25%) may additionally have neurological symptoms including loss of the senses of taste and smell, altered mental state, and headaches.

One of the sources of cognitive impairment observed in COVID-19 patients is the olfactory bulb and its strong connection to the hippocampus that is responsible for memory and cognition. Cognitively- impaired COVID-19 patients may

be the subject of accelerated cognitive decline over time, severe neurological degradation, brain inflammation, and seizures.

Will there be a Lasting Neuropsychological Impact of COVID-19?

COVID-19 is more usually thought to cause potentially irreversible lung damage and associated respiratory problems. In actuality, the damage may extend far beyond the lungs and reach into the brain. Thus, it is entirely plausible that people who have had COVID-19, whether having been asymptomatic or experiencing mild symptoms, may potentially face future neuropsychological problems.

Some researchers think that SARS-CoV-2 respiratory problems may result from two factors: (1) brain stem dysregulation and, possibly, (2) gastrointestinal symptoms. The relationship between these two factors may be understood from the symbiosis between our two interacting brains: the "brain-under-the skull" an the "brain-in-the gut" (for a detailed discussion of these two brains and their interaction, see Fymat, 2020).

The Pathogenic Brain

The presence of pathogens (bacteria, viruses, fungi, and other microbes) in the brain is not new. The additional presence of SARS CoV-2 (Aamodt *et al*., 2020; Braak *et al*.,2004; Cheng *et al*., 2020; Mao *et al*. 2020), if and when identified, should not be surprising. In earlier publications (Fymat 2018 a,b,c; 2019 a,b), I retraced the history of the pathogenic brain back to 1835 in Europe when the connection was made between influenza infection and psychosis. The U.S. epidemic of Parkinson's disease (PD) in the 1940s - early 1950s, was correlated with the 1918 'Spanish' flu epidemic that had been caused by the H1N1 virus (a subtype of the H1N5 virus). In 1974, viral antigens were found in the brains of deceased people affected by *encephalitis lethargica* (Foley, 2009). Speculatively, the condition could be a precursor of PD and other neural dysfunctions. It was noted by several other scientists (Gamboa, 1974; Ogata *et al*., 1997; Braak, 2003; Smeyne *et al*., 2008, 2009). It is not limited only to influenza but extends to several different viruses (measles, herpes, HIV). However, conflicting experimental results prompted a reconsideration of the pathogen connection to, and effects on, the brain and this is what the Consortium mentioned in the Introduction section above has set out to do. In the meantime, it is important to note that whereas viral infection alone may not cause a neuropsychodegenerative disorder (for example, H1N1 may not cause PD), it may however prime the nervous system to other neurological conditions.

Now, the link of the brain to various pathogens is mediated by the loss of impermeability, disruption or even breakdown of the brain protective barriers, particularly the blood-brain barrier – BBB (Fymat, 2018a). Other avenues exist for reaching directly the brain (intra-nasal and sinus access, lingual nerve, vagus nerve, and even the olfactory bulbs). Generally, brain infections by pathogens can lead to transient or permanent neurologic or psychiatric dysfunctions. Microbes in the brain may indicate meningitis or encephalitis, two diseases that are active infections with inflammation. However, for neurodegenerative diseases like PD, AD, and others that were not thought to be infectious, finding pathogens in the brain was both surprising and concerning. Brain infections also involve other parts of the CNS including the spinal cord. They can cause inflammation of the brain (encephalitis), the layers of tissue (meninges) that cover the brain, and the spinal cord (meningitis). Often, bacterial meningitis spreads to the brain itself, causing encephalitis. Similarly, viral infections that cause encephalitis often also cause meningitis. Usually in encephalitis and meningitis, infection is not confined to one area but may occur throughout the brain, within the meninges, along the entire length of the spinal cord, and over the entire brain. Infection may also be confined to one area (empyema in an existing space in the body; abscess).

infectious organisms reach the brain and meninges in several ways by being carried by the blood and traversing the BBB, or entering the brain directly from the outside, or else spreading from nearby infected structures. Sometimes also a brain infection, a vaccine (yes, a vaccine!), cancer, or another disorder may trigger an autoimmune reaction as a result of which the brain becomes inflamed. Encephalitis is most commonly due to viruses (herpes simplex - HS, herpes zoster - HZ, cytomegalovirus - CMV, West Nile virus - WNV, HIV, and prion disease). Will it also be caused by SARS CoV-2?

In addition to the flu-Parkinson connection, other links have been found between viruses and neurological problems (Baig, 2020; Das *et al*., 2020; Heneka *et al*. 2020; Iroegbu *et al*, 2020; Munhoz *et al*., 2020; Tsai *et al*., 2020; Varatharaj *et al*., 2020). Examples abound:

- ***Connection with Measles and Herpes:*** Oligodendrocytes damage in mice and neuron demyelination in multiple sclerosis (MS) patients are similar.
- ***Connection between Human Herpes Viruses (HHV)-6 and -7 Infections and Alzheimer's:*** These viruses spurred the development of the protein amyloid-β which forms plaques – one of the hallmarks of Alzheimer's.
- ***HIV:*** Amyloid-β plaques develop in Alzheimer's. The virus can traverse the BBB, infiltrate the brain, spur neuronal death, cause a loss of synaptic connections, and develop dementia and loss of brain matter that mirrors what is seen in AD (Itzhaki *et al*., 2020). Additionally, HIV-patients also develop slowness in movement and tremors like in PD.
- ***Multiple Sclerosis:*** Induced with herpes virus-6, it has also been tentatively associated with the onset and development of AD.
- ***Memory Deficits:*** Mice infected with certain strains of the flu virus suffered memory deficits even after they seemingly recovered;
- ***Smeyne's experiments:*** Given a low dose of a toxic material (MPTP), mice can be protected against Parkinson-like symptoms by either prophylactic treatment (with a vaccine) or by early treatment (with *Tamiflu*). Extrapolating these results from mice to humans, if valid, the logical conclusion would be that vaccination or treatment with *Tamiflu* may not only treat the flu infection but also help prevent neurodegenerative complications.

It is hoped that the Consortium's research will help develop ways to mitigate the above neuropsychological effects and others. Further, understanding how infections trigger the immune system could lead to ways to down-regulate glia-driven inflammation in preventing long-term damage.

The Gut-Brain Axis

Evolutionarily, since times immemorial, the commensal indigenous microbial communities living in humans have formed an integrated and balanced ecosystem that regulates their physiology in health and disease. Disruptions in this balance can be correlated with neuropsychodegenerative disorders (such as Alzheimer's, Parkinson's, and other diseases). Such disruptions contribute to or modulate these etiology(ies) but are not their cause(s). The bidirectional gut-brain axis (GBA) connects the two brains ("brain-in-the-skull", "brain-in-the-gut"). Mediators of this communication include neurons (vagal afferent, spinal sympathetic), immune pathways, the hypothalamic-pituitary-adrenal axis (HPAA), and metabolic mechanisms. Having traveled along these communication pathways, bacteria, viruses, fungi, and other microbes are part of a growing list of pathogens found in the brains of patients with neuropsychodegenerative diseases. (Bostancıklıoğlu 2020; Gershon, 1998; Fymat, 2019c). As noted in the inroductory paragraph, SARS CoV-2 may also travel along these pathways and likewise contribute to such dysfunctions.

More than in either the spinal cord or the peripheral nervous system (PNS), the second brain contains some 100 million neurons, Just like the brain-in-the-skull, the enteric nervous system is filled with important neurotransmitters (more than 30) to handle multiple functions beyond simple digestion. Further, the vagus nerve carries information unidirectionally from the gut to the brain, playing key roles in certain diseases throughout the body. Nonetheless, despite this far-reaching influence, the gut is not the seat of any conscious thoughts or decision-making processes although it mediates the body's immune response. Charting the gut-brain communication pathway could someday lead us to new treatments for non-neuropsychodegenerative diseases (NPDD) such as autism, inflammatory bowel disease (IBD), irritable bowel syndrome (IBS), obesity, and even disorders once thought to be solely psychological such as anorexia, chronic stress, and post-traumatic stress disorder (PTSD).

Neurotropism and Neurotropic Viruses

Coronaviruses, especially β-coronaviruses that include SARS CoV-2 invade the CNS differently according to a variable degree of ACE2 deficiency. Some neurotropic viruses (mumps, rabies, Epstein-Barr virus - EBV, and SARS CoV-2) cause milder symptoms while others may cause brain swelling, paralysis, and death. Since some flu-like viruses are neurotropic and similar in structure to the novel coronavirus, they can provide insight into long-term effects to expect in people who have recovered from COVID-19. Indeed, since the 'Spanish' flu pandemic of 1918, many of the flu-like diseases have been associated with brain disorders (elevated risk of AD, PD, mental health problems, memory and behavior problems) (Fymat, 2021).

Implications for Various Neuropsychodisorders

Psychiatric Disorders

Like for the SARS CoV-1 epidemic, psychiatric distress and acquired cognitive deficits after COVID-19 will likely cause poor occupational, functional and mental health outcomes, high PTSD levels, and high depressive levels. For those with preexisting psychiatric disorders, the reported symptoms were anxiety, fatigue, insomnia, irritability, traumatic memories, depressed mood, and sleep disorder.

Neuropsychiatric Disorders

Some neurodegenerative disorders (NDDs) are characterized by viral infection such as, for example, olfactory deficits and anosmia. On the other hand, incident and prevalent cardiovascular and cerebrovascular diseases (stroke, coronary artery disease, carotid stenosis, atrial fibrillation, hypertension, and hyperhomocysteinemia) are independent risk factors of dementia. Consequently, COVID-19–related cardiovascular and cerebrovascular disease may also contribute to cognitive decline and dementia. However, COVID-19 related cardiovascular mechanisms are not yet fully established. Nonetheless, based on past pandemic experience with neurotropic respiratory viruses, we should expect neuropsychiatric sequelae (e.g., cognitive decline, motor impairment, affective and psychotic disorders, and demyelinating processes or cerebrovascular disease).

Cognitive Decline and Motor Impairment

High levels of pro-inflammatory cytokines, acute respiratory distress, hypoxia, and neurological manifestations observed in COVID-19 patients will contribute to cognitive decline. Remember also the association between the H5N1 virus and PD attributed to the 1918 'Spanish' flu epidemic. However, it is unclear whether the above two instances are similar. Further, the vascular architectural deterioration by the SARS Cov-2 and other viruses can cause demyelination, neurodegeneration, cellular senescence, and cognitive decline.

Conclusions

SARS CoV-2's impact on the central nervous system may be a prelude to cognitive decline, Alzheimer's disease, and other dementias in later life. The international, multidisciplinary Consortium recently formed to investigate these issues will collect and evaluate their consequences for cognition, and functioning—including the deep biology of Alzheimer's and other dementias. It is hoped that such answers will soon be forthcoming.

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