Current Opinions in Neurological Science
ISSN: 2575-5447

Editorial Article Volume 6 Issue 1 • 2021

On Sars COV-2 Neuropsychiatric Dysfunctions and Sequelae

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Received : January 17, 2021
Published : January 20, 2021

As the COVID-19 pandemic continues unabated, 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. Once the virus enters the body, it usually settles in the cells that line the upper respiratory tract (nose, sinus cavity, and throat), which are the areas commonly targeted by tests for its presence. 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 release syndrome (or 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 cases (Hess *et al*., 2020).

Of importance here are other problems that may affect the central nervous system (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; Wu et al., 2020 a,b) and the later-life cognitive decline associated with Alzheimer's, other dementia-types (Fymat, 2020b), and other neurodegenerative disorders (Naughton et al., 2020; Ogata *et al*., 1997). In this regard, an international Consortium was recently formed to prospectively study some of these effects and the associated risks. With technical guidance from the World Health Organization, and in addition to the Alzheimer's Association, that entity involves representatives from more than 30 countries. It will cover in excess of 22 million COVID-19 cases worldwide (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. These long-term sequelae will further contribute to the global disease burden in coming years. (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 economic, financial, societal, and family and personal effects.)

To be clear, the results from the Consortium's efforts will not generally be unexpected but will provide a more accurate assessment of the nature and extent of the potential neuropsychiatric effects of SARS COV-2. Indeed, the presence of pathogens (bacteria, viruses, fungi, and other microbes) in the brain is not new. Likewise, the presence of SARS COV-2 in the brain (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 (Fymat, 2019 a;b) back to 1835 in Europe when the connection was made between influenza infection and psychosis. Later, the 1918 Spanish flu epidemic caused by the H1N1 virus (a subtype of the H1N5 virus) was correlated with the U.S. epidemic of Parkinson's disease (in the 1940s - early 1950s). In 1974, viral antigens were found in the brains of deceased people affected by *encephalitis lethargica* (Foley, 2009) that was associated with (and some thought caused by) the 1918 Spanish flu epidemic. It was even speculated that the condition could be a precursor to Parkinson's disease. The connection between influenza and neural dysfunction 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 has set out to do. In the meantime, it is important to note that whereas viral infection alone may not cause a neuropsychodegenertive disorder (for example, H1N1 may not cause Parkinson's), it may prime the nervous system to be sensitive to other things that would.

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 (Fymat, 2018a). Other avenues for reaching directly the brain are the intra-nasal and sinus access, the mouth through the lingual nerve, the gut through the vagus nerve, and even the eye through the olfactory bulbs, all of which connect to the brain by replicating and spreading. 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 Alzheimer's (Fymat, 2019d), Parkinson's (Fymat, 2020a), 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 central nervous system including the spinal cord. They can cause inflammation of the brain (encephalitis) and of 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).

But, how do bacteria and other infectious organisms reach the brain and meninges? They can do so in several ways by being carried by the blood and traversing the blood-brain barrier, or entering the brain directly from the outside, or else spreading from nearby infected structures. Sometimes also a brain infection, 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, herpes zoster, cytomegalovirus, West Nile virus, HIV and prion disease). Will it also be caused by SARS COV-2?

The flu-Parkinson connection is not the only link between viruses and neurological problems (Baig, 2020; Das *et al*., 2020; Fymat, 2020a; Heneka *et al*. 2020; Iroegbu *et al*, 2020; Munhoz *et al*., 2020; Tsai *et al*., 2020; Varatharaj *et al*., 2020). Examples abound: (a) Connection with measles and herpes: mice experiments evidenced the same kind of damage to their oligodendrocytes as patients with multiple sclerosis do with demyelination of neurons; (b) HIV patients: developed plaques of amyloid-β like in Alzheimer's (Itzhaki *et al*., 2020)) and can also develop slowness in movement and tremors like in Parkinson's); (c) Memory deficits: mice infected with certain strains of the flu virus suffered memory deficits even after they seemingly recovered; (d) Multiple sclerosis induced with herpes virus 6: has also been tentatively associated with the onset and development of Alzheimer's ; (e) Connection between human herpes viruses 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 (Fymat; (f) HIV: it can traverse the blood-brain barrier, infiltrate the brain, spur neuronal death and a loss of synaptic connections, and develop dementia and loss of brain matter that mirrors what is seen in Alzheimer's; (g) Smeyne's experiments: mice given a low dose of a toxic material (MPTP) 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 if a person gets a pathogen infection, vaccination or at least treatment with Tamiflu may treat the influenza but also help prevent the neurodegenerative complications of influenza infection.

We need to better understand how the brain responds to viral infection long after our immune system has cleared the infection from our bodies. It is hoped that the Consortium's research will help develop ways to mitigate the neuropsychological effects. Further, understanding how infections trigger the immune system could lead to ways to down-regulate glia-driven inflammation in hope of preventing long-term damage.

Separately, and evolutionarily since times immemorial, humans have lived and continue to live in a permanent symbiotic relationship with the commensal indigenous microbial communities living within them, forming an integrated ecosystem. The gut microbiome affects the host's physiology in health and disease. Disruptions in its balanced composition (so-called "dysbiotic states")

can be correlated with neuropsychodegenerative disorders such as Alzheimer's, Parkinson's, and other diseases, contributing to or modulating their etiology(ies) but not being their cause(s). Connecting the two brains (the brain-in-the-skull and the brain-in-the-gut) is the gut-brain axis along which bidirectional communication takes place. Mediators of this communication include neurons (vagal afferent, spinal sympathetic), immune pathways, the hypothalamic-pituitary-adrenal axis, and metabolic mechanisms. Having traveled along the above 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.

The second brain contains some 100 million neurons, more than in either the spinal cord or the peripheral nervous system. Further, just like the brain-in-the-skull, the enteric nervous system is filled with important neurotransmitters (more than 30) to handle much more than mere digestion. Also, about 90% of the fibers in the primary visceral nerve (the vagus) carry information from the gut to the brain and not the other way around. It determines our mental state and plays key roles in certain diseases throughout the body. However, despite its far-reaching influence, it is not the seat of any conscious thoughts or decision-making process. Further, since at least 70% of our immune system is aimed at the gut to expel and kill foreign invaders, the second brain may be mediating the body's immune response.

Charting the gut-brain communication pathway could someday lead us to new treatments for non-neuropsychodegenerative diseases such as autism, inflammatory bowel disease, irritable bowel syndrome, obesity, and even disorders once thought to be solely psychological such as anorexia, chronic stress, and post-traumatic stress disorder.

In summary, as the COVID-19 pandemic continues unabated, we are learning more about its short- and long- term effects on the body. Once the virus enters the body, if not subdued by the body's immune system, it can lead to a variety of disorders and dysfunctions and may hinder or even overcome the immune system. An overblown immune system may cause a cytokine storm, attacking healthy tissues and leading to low blood pressure, blood vessel damage, organ damage or failure, heart problems, and neuropsychiatric disorders. The latter dysfunctions will be examined in a prospective study by a newly formed international Consortium. The anticipated results from this study will be highly important in better understanding the short- and long-term effects of SARS COV-2 on the 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 contributors, 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.

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