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Development of Schizophrenia in a Genetically Predisposed Individual Following COVID-19

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ROWAN-VIRTUA School of Osteopathic Medicine

Project title

Development of Schizophrenia in a Genetically Predisposed Individual Following COVID-19

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Background

The risk factors and related markers in the development of psychosis have traditionally relied strongly on components such as age, gender, and hereditary predisposition, including the number and type of affected family members, as well as environmental factors such as negative psychosocial influence and frequent early age use of cannabis. For instance, higher rates of occurrence are seen in men at approximately 1.4 males for every 1 female; the average age of onset for males usually occurs during their early 20s, and in females by their late 20s; Risks increasing from 10% to 40% for each additional affected parent, all of which suggest a strong genetic link. [1]

Recently, however, there have been an increasing number of cases reporting COVID-induced psychosis or COVID-related psychosis, drawing attention towards alternative etiologies that suggest a two-hit mechanism, or the 'priming' of the immune system prior to the onset of disease. We discuss the the two-hit hypothesis in the development of schizophrenia secondary to COVID-19, and explore its proposed pathophysiology, including the process of synaptic pruning as a direct result of the sequelae of neuroinflammation due to cytokine hyperactivity. [2]

Case Presentation

We present a patient who is a 56-year-old female with a psychiatric history of anxiety disorder and a medical history of hypercholesterolemia and hyperthyroidism, who was admitted to the hospital after a witnessed seizure at an inpatient psychiatric facility.

In March 2020, the patient presented to the Emergency Department (ED) for evaluation of shortness of breath that started several weeks prior. The patient was admitted to Intensive Care Unit on 3/21/2020 for an unstable condition with a temperature of 101.4 F, 125 heart rate, 41 respiratory rate, and blood pressure of 165/113 with a diagnosis of bacterial pneumonia superimposed on viral pneumonia. The patient tested positive for COVID-19. After 7 days of hospitalization, the patient was discharged. Upon discharge, the patient followed up with her primary care provider and her endocrinologist, who recommended continuing her routine medications, including Buspirone 10 mg daily, Hydroxyzine 50 mg every 8 hours as needed, Alprazolam 0.25 mg nightly as needed. Alprazolam was increased to 0.5 mg nightly in September 2022.

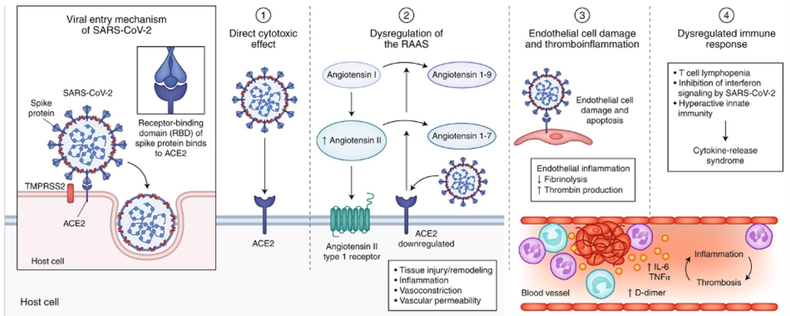
In June 2022, the patient saw a neurologist for ringing in her right ear for 3 months, headache, and dizziness, for which she was diagnosed with tinnitus. MRI of the brain was unremarkable. When she followed up with the neurologist in November 2022, the headache and dizziness resolved but the ringing in her ears appears to have persisted.

On December 12, 2022, her nephew brought the patient into the ED for psychiatric evaluation for paranoia and hallucination that started several months ago. The patient reportedly locked herself in a bathroom and screamed "Get out. They're spying on me." At the ED, tests were only remarkable for a positive urine drug screening for benzodiazepines. The patient was involuntarily admitted to an inpatient psychiatric hospital on December 14, 2022, and started 50 mg of Quetiapine for further stabilization. After 30 seconds of witnessed seizure, the patient was transferred to a different hospital for medical stabilization. During her stay on the medical floor, she was resumed on 50 mg of Quetiapine, which was eventually increased to 100 mg nightly. The patient describes that she had a "nervous breakdown", admitting to hearing multiple voices, though she was unable to elaborate on the content of what she was hearing. Additionally, she reported poor sleep due to the voices that prevent her from falling asleep at night. After 6 days on the medical floor, she became medically stable for discharge back to her inpatient psychiatric hospital.

According to collateral obtained from the patient's nephew, she began exhibiting paranoia toward her neighbors shortly after she was discharged from a COVID-related hospitalization in March 2020. The patient believed the neighbors were listening to her thoughts through her windows and walls and sending her "radio waves", causing her feel unsafe and eventually lock herself in the bathroom. Of note, the patient had not exhibited any signs or symptoms of psychosis prior to COVID-19. The nephew also reported a family history of mental illness although he was unsure of the exact diagnosis, stating that the patient's mother had been hospitalized twice approximately 40 years ago at an inpatient psychiatric facility for auditory hallucinations. The patient's mother is not currently on any psychotropic medications and it is unclear which medications she had taken prior for her past psychiatric events.

Pathophysiology of Coronavirus Disease 2019 (COVID-19)

The virus enters cells via the angiotensin-converting enzyme 2 (ACE-2) receptor. Once internalized in the cell, the virus goes through replication and maturation, which then results in an inflammatory response that involves the activation of immune cells by cytokines. COVID-19 can result in damage to multiple organs because the ACE-2 receptor is present throughout the human body, including in the oral and nasal mucosa, lungs, heart, gastrointestinal tract, liver, kidneys, spleen, brain, and arterial and venous endothelial cells. [3]

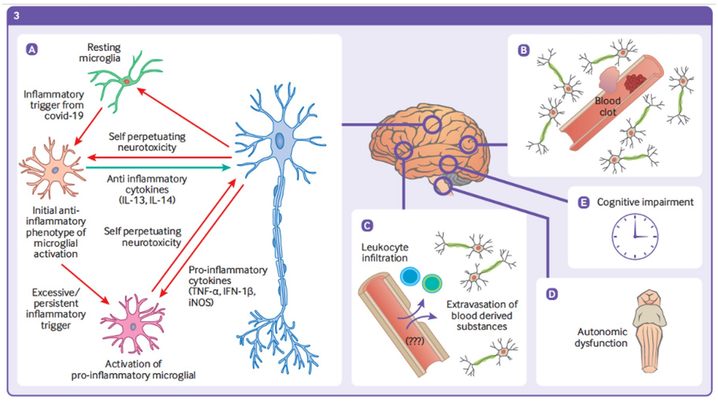


COVID - 19 on Cognition and Mental Health

- Patients admitted to the hospital with COVID–19 present diverse neurological symptoms including encephalopathy, cognitive impairment, cerebrovascular events/disease, seizures, hypoxic brain injuries, corticospinal tract signs, and altered mental status. "Brain fog" is described to be the most common symptom.[3]
- Delirium seems to be related to critical illness, severe acute respiratory syndrome, and long-term ventilator support.[3]
- COVID – 19 along with quarantine, isolation, and social distancing have negatively affected mental health conditions including post-traumatic stress disorder (PTSD), depression, anxiety, and obsessive-compulsive symptoms following recovery from the acute infection.[3]

Mechanism of Action of COVID on Mental Health

Coronavirus can infect the central nervous system (CNS) via hematogenous or neuronal retrograde neuro-invasive routes. Another possible mechanism is that COVID may affect the permeability of the blood-brain barrier, which would inevitably introduce peripheral cytokines into CNS. [3] Virus can cause various conditions, including but not limited to septic encephalopathy, non-immunological effects, immunological effects such as microglial activation and a maladaptive cytokine profile.[4]



Two-Hit Hypothesis and COVID

The development of schizophrenia has been historically viewed through the 'first hit' lens, suggesting that genetically predisposed individuals are more likely to develop this condition. A newly emerging concept of the two-hit hypothesis, however, suggests the development of schizophrenia is a result of both environmental insults and genetic predisposition, leading to the priming or sensitization of the immune system prior to its activation later in life.[5] These environmental insults can be multifactorial in etiology, but nonetheless involve the activation of pre-sensitized microglial cells and consequent neuroinflammation. It is suggested these activated microglial cells then participate in a process of synaptic pruning, ultimately resulting in the development of aberrant synaptic pathways.[2]

In a normal healthy brain, microglia are highly motile and undergo remodeling processes to help support neuronal plasticity and in the remodeling of neuronal circuitry. They participate in these remodeling processes by removing cellular debris through phagocytic processes. [2] In the pathologic processes of schizophrenia, however, there are alterations to microglial cell activity, including increased cellular turnover and increased activity, especially within the frontal and temporal lobes.[6] This hyperactivity and increased turnover rate are likely implicated in the impairment typical neuronal structure and functioning found in the healthy brain.

Although several documented long-term psychiatric conditions have emerged as a result of COVID-19 infection, including post-traumatic stress disorder (PTSD), depression, anxiety, and obsessive-compulsive disorder (OCD), we suggest the strong plausibility in the development of Schizophrenia too, through shared mechanisms of neuroinflammation and glial cell activation. The current research on the sequelae of post-COVID-19 neuropsychiatric symptoms are attributed to excessive pro-inflammatory processes, including the persistent provocation of glial cells via cytokines such as TNF-alpha, IFN-1B, and iNOS, ultimately leading to the damage of neurons via glial activation. [3]

Conclusion

Through the constructs of the two-hit hypothesis, our 56-year-old patient likely developed primary schizophrenia as a combination of her genetic predisposition and her COVID-19 infection. Although her age remains an outlier for her late presentation of primary schizophrenia, her family history of her mother's unspecified psychotic disorder strongly supports her genetic predisposition of disease, and likely serves as the 'first hit', and her development of COVID-19 and subsequent inflammatory cascade representing the 'second hit'.

References

1. Kringlen E. Twin studies in schizophrenia with special emphasis on concordance figures. *Am J Med Genet*. 2002; 97(1): p.4-11. doi: 10.1002/(sici)1096-8628(200021)97:1<4::aid-ajmg2>3.0.co;2-j
2. Tremblay, M. È., Stevens, B., Sierra, A., Wake, H., Bessis, A., & Nimmerjahn, A. (2011). The role of microglia in the healthy brain. *The Journal of neuroscience : the official journal of the Society for Neuroscience*, *31*(45), 16064–16069. https://doi.org/10.1523/JNEUROSCI.4158-11.2011
3. Crook, H., Raza, S., Nowell, J., Young, M., & Edison, P. (2021). Long covid-mechanisms, risk factors, and management. *BMJ (Clinical research ed.)*, *374*, n1648. https://doi.org/10.1136/bmj.n1648
4. Needham EJ, Chou SH, Coles AJ, Menon DK. Neurological Implications of COVID-19 Infections. Neurocrit Care. 2020 Jun;32(3):667-671. doi: 10.1007/s12028-020-00978-4. PMID: 32346843; PMCID: PMC7188454.
5. Feigenson, K. A., Kusnecov, A. W., & Silverstein, S. M. (2014). Inflammation and the two-hit hypothesis of schizophrenia. *Neuroscience and biobehavioral reviews*, *38*, 72–93. https://doi.org/10.1016/j.neubiorev.2013.11.006
6. Blank, T., & Prinz, M. (2013). Microglia as modulators of cognition and neuropsychiatric disorders. *Glia*, *61*(1), 62–70. https://doi.org/10.1002/glia.22372