

SARS-Cov2-Induced Cytokine Storm and Schizophrenia, Could There be a Connection?

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Abstract - Today, a new coronavirus (2019-nCoV, later named SARS-CoV-2) has become known as a pandemic with over 3,949,200 cases and 271,782 deaths. It has been considered that most of the deaths in infected patients stem from comorbidity conditions. Therefore, understanding at-risk populations are currently under the focus of investigations. This object has highly driven attention to put patients with a higher potential of death related to SARS-CoV2 infection at priority. For instance, this can happen in Schizophrenia owing to ambiguous immunology attributes, including elevated levels of pro-inflammatory cytokines and stress-related immune disability. Given that, the hyper-inflammatory responses are the significant cause of the pathophysiology of the SARS-CoV2-related mortality. Moreover, SARS-CoV2 can prompt the risk of developing Schizophrenia in the future. This review punctuates that prenatal/perinatal infection could be associated with increased Schizophrenia risk; on the flip side, the potential risk of ongoing medication can worsen mentally disabled patients, and healthy people are at risk.

Keywords: COVID-19; SARS-CoV-2; inflammation; schizophrenia; olfactory cells

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Introduction

Late 2019 was the beginning of a tragedy that impacted economies, health, and lifestyle [1]. Since May 08, 2020, more than 3,949,200 confirmed Coronavirus Cases with 271,782 deaths had been reported worldwide. SARS-CoV2 is an infectious disease caused by the family of coronavirus. The virus profoundly causes malfunctions in the pulmonary, heart,

kidney, and digestive systems. It severely damages the brain [2], which is inferred as a new host for the virus, e.g., experiencing anosmia for months is commonly reported as the symptom of Covid-19 [3,4]. Clinical investigation on SARS-CoV2 patients demonstrates that after the virus invasion, body reaction relegated into two waves of cytokines lead by innate and adaptive immune cells [5]. The clinical survey also revealed that SARS-CoV2 increases innate immune cells, including neutrophils, and decreases cellular immune cells, particularly T cells. The storms of cytokines lead by pro-inflammatory factors comprising IL-6 and IL-1, which targets therapeutic con-

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sequences [6,7]. For example, clinical trials on Anti-IL-1 Agents Canakinumab and Anti-IL-6 Agents Sarilumab, Siltuximab [5,8-11].

Dysregulation of inflammatory response is observed in various psychiatric diseases such as Graves' disease, Depression, active inflammatory bowel disease (IBD), rheumatoid arthritis (RA), Multiple Sclerosis (MS), and Schizophrenia [12-14]. Schizophrenia is a chronic form of psychotic, affects around 1% of the population worldwide, with mental symptoms including working memory impairment, inability to sustain attention, and executive functions [15]. Schizophrenia and the immune system interaction have been studied extensively [16-19]. As an illustration, pro-inflammatory cytokines in the peripheral blood of Schizophrenia patients with first-episode and relapsed are significantly high [20]. The elevated serum concentrations of IL-6 and other pro-inflammatory cytokines, including IL-1 β , interferon γ , TNF α , and decreased serum concentrations of anti-inflammatory cytokines such as IL-10, were found to be related to increased risk of Schizophrenia [19]. A study of the Parents and Children birth cohort found that the higher serum concentration of IL-6 at age 9 is related to a twofold enhanced risk of psychotic disorder at age 18 [21]. It should be considered that no study has been carried on the potential role of inflammatory signaling in Schizophrenia and possible vulnerability to SARS-CoV2 infection. This review discloses the perspective evidence of the increasing schizophrenia-like symptoms due to over-prescription of hydroxychloroquine and chloroquine in response to SARS-CoV2 and recounts that SARS-CoV2 itself can cause Schizophrenia in infected children. Besides, the current Schizophrenia patient is exceedingly vulnerable to SARS-CoV2 due to already high interleukin features.

Schizophrenia and COVID-19: risks and recommendations

Patients with a psychiatric disorder, including Schizophrenia, typically experience con-

stant stress and anxiety at different levels. This phenomenon enforces transient/steady manipulation in the body, especially the immune system. Aside from regular Schizophrenia rebellious attributes, such as disorganized behavior, delusion, and lower awareness of the risk of SARS-CoV2, other factors, including the presence of comorbidity condition, e.g., diabetes, chronic respiratory disease, cardiovascular disease, and immunological abnormalities, are also the critical factors to exacerbate the SARS-CoV2 situation [22,23]. To illustrate, a common stressor, for example, academic exams could suppress cellular immunity; meanwhile, chronic cases tend to suppress both cellular and humoral immune cells [24]; of note, pro-inflammatory cytokines increase in response to acute stress [25]. Generally, pressure and the disease related to stress raise IL-6 levels in serum [26]. Some antipsychotic drugs, especially clozapine, can profoundly trigger the risk of death from pneumonia through hypersalivation [26]. It clarifies the tragic infection responses such as cytokines inhibit clozapine metabolism and increase their concentration in the serum, resulting in hypersalivation and arrhythmia [27]. In addition, clozapine itself can increase the risk of COVID-19 infection [28,29].

Cytokine-Storm and Schizophrenia

There is a famous theory that patients with severe mental illness suffer impaired immune systems. This notion mainly stems from a few phenotypic/genotypic features, i.e., not only that studies have proven that there is genetic linkage among Schizophrenia and immune-related genes such as major histocompatibility complex (MHC), cytokines itself control neural development that can overall impact on behavior brain structure [30-32]. Having shared immunodeficiency is not almost constrained to Schizophrenia; also, other psychotic diseases show it either, e.g., elevated plasma IL-10 levels in patients with bipolar disorder are typical. However, the cytokine profile in Schizophrenia is broader with high levels of interleukin (IL)-1 β , IL-2, IL-6, interferon (IFN)- γ and

IL-8 [33,34]. Likewise, there are reports of the first episode and increasing cytokines, namely IL-10, soluble IL-2 receptor (sIL-2R) [19].

Further study on brain structure and cytokines showed that cytokines' influence on brain development is more comprehensive than what already expected to illustrate, IFN- γ . IL-6 and IL-12 levels in schizophrenia plasma inversely influence percent whole-brain gray matter, particularly IL-6 and hippocampal gray matter volume [35]. In addition, reports and hypotheses on relationships between peripheral IL-1 β mRNA and verbal fluency in people with Schizophrenia and decreased Broca's area volume doubly reinforce the correlation between the immune system and brain development [36].

Virus and Advent of Psychiatric Disorder

Virus entry manipulates gene regulation depending on the type of cells, cellular timing, and age. To illustrate, in neuron cells, especially in the prime period of life, such as childhood and fetus, the central nervous system (CNS) is in a delicate time due to rapid brain development. Various viral infections can increase the risk of Schizophrenic-like symptoms, either during pregnancy or after birth (Table 1). The method of involving viruses in the CNS is interpreted by imposing chaos in the array of protein interactions regarding existing homologous proteins among the viruses and protein of schizophrenia-related genes; This contribution may lead to neuropsychiatric dis-

ease etiopathology [37]. A study on the coronavirus family has revealed that coronaviruses like influenza could be neurotropic; a further survey on people with a mental health condition showed all four strains of coronavirus (229E, HKU1, NL63, and OC43) was prevalent in 106 patients with onset of psychotic symptoms. Among them, NL63 was virtually associated with schizophrenia-spectrum [38]. The timing of infection is so critical, probably because genes activate in different circumstances. Due to that, the viruses were subdivided into two categories. An instance of the timing of infection is the Epstein-Barr virus (EBV), which typically infects in early adolescence. However, it can also happen in children and adults, while many other viruses are generally infected in childhood [39]. Indeed, other viruses also support the theory of virus effect on brain development, including Toxoplasma and Cytomegalovirus (CMV). An extensive study on 81,912 individuals indicated that immunoglobulin G (IgG) antibodies against Toxoplasma and cytomegalovirus (CMV) were significant among those who suffer from psychiatric issues; 25.9% of the population was associated with Schizophrenia and CMV influenced 60.8 % of the population. The latter group is prone to showing psychiatric disorder with slightly neurotic, somatoform, and stress-related symptoms and attempting or committing suicide. These studies reinforced the idea that there is a causal relationship between the virus and psychiatric disorders [40].

Table 1. Viruses with the capability to affect brain development and onset symptoms of Schizophrenia

Life cycle	Virus
Pregnancy (prenatal) (maternal infection can risk fetus mental health)	Common cold with fever [95], rubella [96], influenza [97], poliovirus [98], measles, varicella-zoster [99], HSV-2 [100], influenza B [101], toxoplasmosis [102]
Neonatal (perinatal) (other viruses in the potential of exerting schizophrenia-like symptoms)	Cytomegalovirus [103], coxsackie B5 [104], childhood meningitis [105], borna [106], measles [107], hepatitis C [108], HIV [109] and toxoplasmosis [110].

COVID-19 neuronal transport

Olfactory impairment is a typical result of prevalent viral infections such as common cold, influenza, and influenza-like illness. Moreover, herpes and hepatitis could be a cause of it. Olfactory nerves and fibers transmit data from the peripheral olfactory system directly to the brain (central olfactory system); olfactory neurons provide a straightforward route for viruses to invade the brain [41]. There are two susceptible tragedies for brain infection; first, blood-brain barrier (BBB) dysfunction; second, olfactory infection. Aside from cytokines' adverse effects on BBB, this tissue highly expresses ACE2, a typical coronavirus receptor, therefore as viremia infiltrates into the bloodstream and reaches BBB, they can directly make damages and eventually rid protection [42], such a trajectory has been proven in Hepatitis E Virus [43], HSV [44] as well.

The olfactory nerves are another way of brain access. It branches from CNS and spread into the respiratory tract, so if the virus infects the olfactory, it can achieve CNS [45,46].

Further evaluation on mice models showed that coronavirus profoundly uses the olfactory system to enter CNS [46,47]; this approach starts after the virus binds to its receptor (ACE2) on the olfactory dendritic then viremia wend to CNS by trans-synaptic transferring. Besides, the situation is worse as the SARS virus treads CNS considering glial cells and neurons also express ACE2 receptors (figure 1) [48]. Of note, neurological manifestations render disorders that can remain years after recovery.

Behavior and Inflammation

IL-1 α and IL-1 β , a couple of potent pro-inflammatory cytokines, bind and activate the

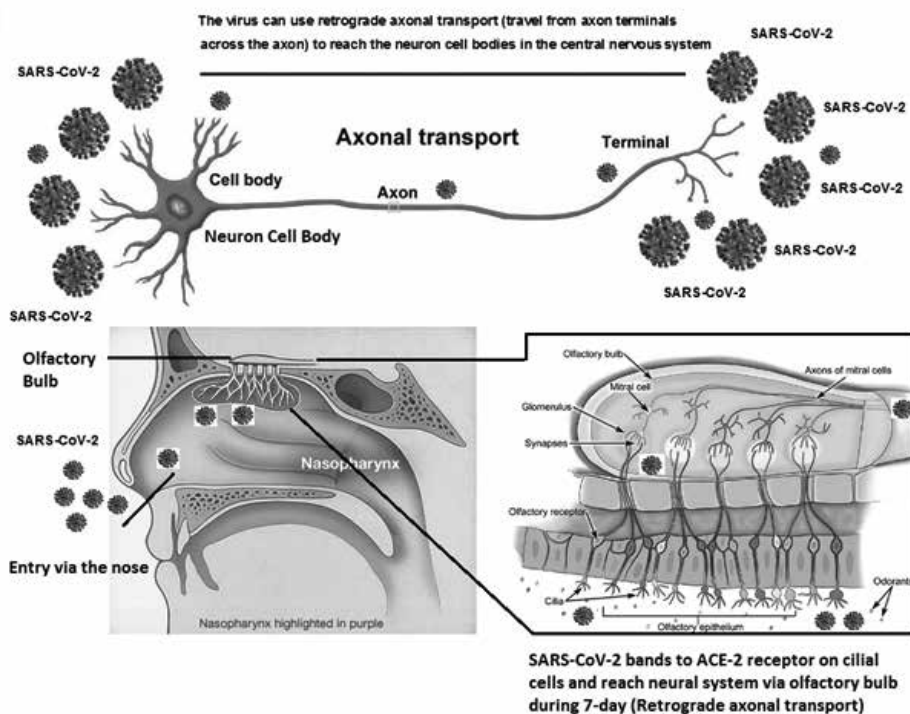


Figure 1. Schematic view of neural transport of SARS-CoV-2

same receptor, are crucial for host-defense responses. They induce the release of other pro-inflammatory cytokines, including TNF and IL-6 [49]. IL-1 β is produced and secreted as inactive precursors (pro-IL-1) by various immune system cells, such as monocytes, macrophages, B-lymphocytes, and NK cells, as well as dendritic cells [50]. Beyond resistant characteristics, IL-1 β and its antagonist IL-1Ra have been extensively described for their ability to act within the CNS [51,52]. For example, it is essential during learning and memory processing [53], and the low dose of IL-1 β could potentially boost hippocampal-dependent memory functioning concerning learning and memory consolidation [54,55]. Notwithstanding, increased levels of IL-1 within the hippocampus produced impairments in spatial memory and long-term contextual fear memory [56]. This level is associated with aging, which is increased in older adults [57]. Furthermore, high levels of IL-1 β on plasma are a commercial feature of male Schizophrenia, especially in the early days, which is frequently called “first-episode” [58].

Synthesis and release of IL-1 in response to SARS-CoV 2 occur after the virus and Toll-Like Receptor (TLR) binding. Activation of TLR2, TLR3, and TLR4 receptors causes a biochemical cascade that begins with the production of pro-IL-1 and following cleavage by caspase-1 [59-61]. IL-1 β is then secreted outside the macrophage, mediating lung inflammation, fever, and fibrosis and provoking severe respiratory problems [62]. Microglia and astrocytes release IL-1 β , increased levels of IL-1 β are related to illness symptoms such as social withdrawal and cognitive impairment in Schizophrenia. Besides, cytokines, e.g., IL-1 β , can cross the blood-brain barrier (BBB) and cause cognitive deficits in Schizophrenia [63]. An animal model study showed that high levels of IL-1 β could cause a significant mitigate in the brain dopamine concentration, similar to what undergoes in Schizophrenia [64,65].

Interleukin-6 (IL-6) is a multifunctional cytokine that modulates the immune system and affects the CNS, secretes by various cell types

such as B cells, macrophages, monocytes, and the CNS, produced by astrocytes, microglia, and neurons [66]. The signaling transduction of IL-6 is induced by binding to its membrane-bound α -receptor and IL-6R, leading to dimerization of its β -receptor gp130. IL-6 can also be activated through the soluble form of IL-6 receptor (sIL-6R), formed by alternative splicing of gp130 mRNA and exerts its influence via PI3K, MAPK, and Jak/STAT pathways [67]. IL-6 expression and microglia activation will be elevated together with other inflammatory markers, including IL-1 β and TNF α , which cause inflammatory neuron responses. High concentrations of the circulating IL-6 in childhood have been observed to be related to increased risk of depression and subsequent psychosis [21]. A growing number of studies suggests that stress can influence cytokines level. To elaborate, overproduction of IL-6 induced by inflammation and aging may mediate impair cognitive processing, e.g., memory and spatial learning in humans [68-70].

Furthermore, enhanced IL-6 levels promote neurogenesis and gliogenesis [71,72]. The dual role of IL-6 in cognition may rely on various factors, including its expression levels, the specific cognitive task, active brain regions, timing, and duration of exposure [73]. A lot of aged-associated diseases, particularly type 2 diabetes, cardiovascular, hyperglycemia, and Alzheimer's disease, are related to the level of pro-inflammatory factors and *vice versa*, such as age-related memory impairments [74-79]. Further studies showed that people situated in weak community interaction have significantly enhanced IL-6 [80]. Increased level of IL-6 was also seen in major depression, bipolar mania, and Schizophrenia. The point mentioned above explains a significant level of pro-inflammatory factors, particularly IL-6 around the CNS [81]. As a natural response to stress, schizophrenic patients and the depressed or healthy person with a stressor situation tend to have elevated levels of IL-6. Surprisingly, the levels of IL-6 in Schizophrenia decreased after remission [82]. Investigating the direct effects of coronavirus

Table 2. Available literature on the association of COVID 19 and Schizophrenia

Study ID	Country	Target group	Study design	Comorbidity	Reference
DERR1-10.2196/19203	USA	352	Telephone interview	Mental illness (schizophrenia, bipolar disorder)	[111]
NA	China	51	Clinical documents	Schizophrenia	[112]
NA	USA	184	NA	Clozapine-treated Schizophrenia	[113]
NA	UK	3559	Systematic review	Psychiatric and neuropsychiatric presentations	[114]
NA	Germany Ireland	1	Physical and Laboratory testing	Schizophrenic	[115]
NCT04498416	France	70 (Recruiting)	Cohort	Mental Disorder	https://clinicaltrials.gov/
NCT04445324	Canada	48	Interventional	Psychotic Disorders Anxiety Depression	https://clinicaltrials.gov/

infections on mental health is the subject of several ongoing studies (Table 2).

Discussion

Elevated B cells, diminished T cells in the blood, and cerebrospinal fluid (CSF) are specific characteristics of Schizophrenia immune cells [83]. Ample research represented the pivotal role of T cell-derived IL-4 in cognitive functioning, learning, and memory regulation by affecting meningeal myeloid cell activation. In simple terms, a high point of T cells in the meninges and depletion of T cells from meningeal spaces resulted in learning and memory impairments [84]. It is suggested that increasing T-cell immunity might be helpful for aging-associated memory issues [85]. A recent study on evaluating coronavirus anti-strains antibodies in patients with new psychotic symptoms revealed the potential of human corona-

virus to use neuron cells as a host. To conduct the notion, the increased number of mental disease reports of SARS-CoV 2 patients is related to the fact that this virus can stay in the brain for time [86]. Chloroquine and hydroxychloroquine, common drugs for the treatment of malaria [87], have been widely prescribed for SARS-CoV2 patients. Although with positive outcomes, on the blindside, they possibly can cause a wide range of side effects on a spectrum of neuropsychiatric manifestations, including paranoia, mania, confusion, hallucinations, agitation, insomnia, depression, psychosis, and suicidal ideation [88], even in the patients without any history of mental illness [89,90]. Comprehensive analyses on people with recent onset of psychotic symptoms demonstrated that they are more susceptible to SARS-CoV2 [91]. Therefore, probable perspective tragedy can be predictable for adults and children after the current outbreak. As

elucidated, infant viral infection is hazardous and increases the risk of inferior brain development following Schizophrenia in the future. Environmental factors such as births in winter and prenatal/perinatal infection have increased Schizophrenia risk. It seems Schizophrenic patients are at tremendous risk of SARS-CoV2 and probably with inferior outcomes with severe symptoms regarding common clinical comorbidities in this illness. Schizophrenia appears to have already activated pro-inflammatory factors, whereas, in most people, these factors were activated only when there is a risk of infection. Elucidated hallmarks demonstrated that they contribute to a shared genetic risk background of vulnerability for SARS-CoV2 and may theoretically jeopardize the health of Schizophrenic patient more than healthy people. It has also been confirmed that the immune system can modulate functional brain capability, behavioral processes, and immune-brain interactions that influence neural development and function, which might have causal and therapeutic implications for various disorders [92-94]. This review highlights that the probable leak of pro-inflammatory cytokines into the brain can be a new reason for the high ratio of depression in SARS-CoV2 recovered patients and the outlook of crowd depression leap in the future.

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Collectively, Schizophrenia is associated with the highest vulnerability to infections considering afflicted immune responses towards pathogens. This contagious disease causes concerns about public physical health and causes or exacerbates several psychological illnesses such as Schizophrenia. In these circumstances, maintaining people's mental health with Schizophrenia is essential because they may experience stressful stimuli in different parts of society during the COVID-19 outbreak. Therefore, in the current high-risk situation, it is necessary to identify people prone to psychological disorders such as Schizophrenia at different levels of society whose mental health may be endangered to maintain mental health with appropriate psychological strategies and techniques.

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Conflict of interest

None to declare.

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Citokinska oluja izazvana SARS-Cov2 i shizofrenija, postoji li povezanost?

Sažetak: Novi koronavirus (2019-nCoV, kasnije nazvan SARS-CoV-2) uzrokovao je pandemiju s preko 3 949 200 potvrđenih infekcija i 271 782 smrtnih slučajeva. Smatra se da većina smrtnih slučajeva među zaraženim pacijentima proizlazi iz komorbiditeta. Stoga je razumijevanje rizičnih populacija trenutno nužno, te se u središtu istraživanja nalazi pacijent s većom potencijalnom stopom smrtnosti. Primjerice, do toga može doći i u oboljelih od shizofrenije zbog nejasnih imunoloških pretpostavki, uključujući povišene razine proupalnih citokina i sa stresom povezano oštećenje imuniteta. Uz navedeno, valja spomenuti kako je prekomjeren upalni odgovor značajni patofiziološki moment mortaliteta povezanog sa SARS-CoV2. Štoviše, SARS-CoV2 može povećati rizik od razvoja shizofrenije u budućnosti. Ovaj pregledni rad naglašava to da bi prenatalna/perinatalna infekcija mogla biti povezana s povećanim rizikom za razvoj shizofrenije. S druge strane, potencijalni rizik od uzimanja kontinuiranih lijekova može pogoršati zdravstveno stanje psihičkih pacijenata, a ugroženi su i zdravi ljudi.

Ključne riječi: COVID-19; SARS-CoV-2; upala; shizofrenija; olfaktorne stanice

