Neurotropic Manifestations as a Potential Risk Factor for Schizophrenia Following in utero Exposure to SARS-CoV-2

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Abstract

Background: COVID-19 infection is associated with neurologic and psychiatric morbidity that suggests a direct effect of the virus or secondary effect of an inflammatory process. These neuropsychiatric consequences may increase the likelihood of schizophrenia in the offspring of women who become infected with COVID-19 during their pregnancy.

Methods: We performed a directed narrative review of the literature focusing on the proposed pathophysiological processes that lead to schizophrenia and known pathological consequences of COVID-19 infection.

Results: Schizophrenia in adult offspring has been associated with maternal infections during pregnancy by a wide range of respiratory and neurotropic pathogens. Spikes in the incidence of schizophrenia approximately 20 years after several influenza pandemics have been documented. There are multiple lines of evidence suggesting that a similar pattern may be seen due to the recent COVID-19 pandemic. These include the nonspecific consequences of acute illness and hyperpyrexia, as well as more specific derangements of brain development related to direct effects of the virus or secondary effects of the inflammatory response on the developing brain. There is the potential to prospectively test this hypothesis by following the offspring of women who are known to have developed COVID-19 during their pregnancy.

Conclusion: The COVID-19 pandemic is likely associated with a range of future neuropsychiatric consequences in people whose mothers suffered the infection during their fetal development. It is important to try to follow these offspring to determine the full range of consequences of COVID-19 infection.

Introduction

Schizophrenia is a severe psychiatric illness that manifests with persistent deficits in motivation, cognition, and executive function, with intermittent episodes of psychosis manifesting with delusions and/or hallucinations. Despite its low prevalence of 0.33–0.75% among non-institutionalized individuals worldwide [1, 2], it is one of the top 20 leading causes of disability across the globe.[3] In the United States, the prevalence lies between 0.25% and 0.64%.[4–6] It is typically diagnosed in the late teens to early thirties [7, 8], but it is suspected that the initial insult occurs in the prenatal period or early in life, with consequent disruptions in the development of the brain.[9]

One of the leading models regarding the pathogenesis of schizophrenia is the infection hypothesis.[10, 11] The body of evidence supporting this hypothesis, while almost exclusively indirect and associational, is nonetheless substantial.[10–12] Briefly, it is proposed that the mother’s exposure to a neurotropic organism during the second trimester of pregnancy may interfere with proper development of the frontal cortex or mesocortical pathways. These structures begin to myelinate in the early teen years and do not complete maturation until age 24 or so.[13, 14] Consequently, even though the damage has already occurred in early development, clinical manifestation of the illness is delayed until adolescence or early adulthood. A spike in the incidence of schizophrenia among the children of women who were pregnant during the 1918–20 influenza pandemic [12, 15] has been central to the hypothesis. More recent understanding of post-infectious inflammatory changes and other environmental factors shed light on potential mechanisms.[11, 12, 16] Now, with a new viral pandemic of COVID-19 [17], we have the opportunity to examine this question prospectively.

To begin this process, we will re-examine the data regarding
neurotrophic changes caused by various organisms and the inflammatory pathways that may be involved. We will further examine the proposal that in utero possibly direct exposure to COVID-19 [18] may play a role in the pathogenesis of schizophrenia, as has been suggested by some authors.[18, 19]

The is a guided narrative review and is not meant to be exhaustive or systematic.

Methods

We performed a directed narrative review of the literature. We focused on previous work that linked pathophysiology of neurotropic infections to subsequent development of schizophrenia in some individuals and searched for similar pathological processes with COVID-19 infection to determine the likelihood of similar outcomes with intrauterine exposure to this virus. Only PubMed was queried. We used the terms “schizophrenia”, “infection”, “exposure”, “viral”, “COVID-19”, “neutropism”, “neuropathology”, and “Maternal Exposure” in different combinations to retrieve relevant articles. The terms were chosen for their relevance and generalizability. No time frame was set on search parameters. Initial title review included relevant articles only according to title. We focused on previous work that linked pathophysiology of neurotropic infections to subsequent development of schizophrenia in some individuals. We then extended our search for similar pathological processes with COVID-19 infection to determine the likelihood of similar outcomes with intrauterine exposure to this virus. Identified articles were read for content by all the authors. The sections in this article were synthesized from the identified articles with additional background data added for clarification. Citations in identified articles were also browsed for relevant data and were included where appropriate.

Results

Our initial search yielded 755 articles. Title review excluded most of these articles, leaving 79. These articles were further refined by abstract and content review to result in 51 articles that were included in the current review. An additional 25 articles were included from the citation review. Finally, 24 articles were added for background information.

Pathogenesis of Schizophrenia

Role of infections

Schizophrenia is a severe mental illness that manifests as a triad of symptoms: positive symptoms of psychosis (delusions or hallucinations) that are episodic superimposed on negative symptoms of blunted affect, avolition, alogia, asociality, and anhedonia that are chronic, and cognitive dysfunction that is progressive. Risk for onset of the illness begins in early adolescence and peaks in late adolescence and early adulthood. There are many factors that have been associated with increased risk of occurrence of this disorder, which include genetic, environmental, and socio-economic; medical, such as issues during pregnancy or subsequent brain injury; and substance use. Many researchers believe schizophrenia may be a group of brain diseases with similar clinical presentations.

Neurotropic viruses that have been linked to psychosis include herpesviruses, retroviruses, influenza, and enteroviruses.[19–25] Viruses are known to enter the brain via direct invasion of the neuronal cells by binding to the peripheral axons and occupying the retrograde transport mechanism or to gain entry via binding to the olfactory neurons. They are also known to gain entry via infected leukocytes crossing the blood-brain barrier (BBB).[26] Exposure to these pathogens in the prenatal period or infancy, and possibly even in childhood or early adolescence, may result in psychosis. In particular, respiratory infections during the second trimester are associated with increased risk of the vertical transmission of these pathogens. Alternatively, hyperthermia, a common manifestation of infections, is known to cause neural tube defects in animal models and has been associated with increased risk of schizophrenia in offspring if a mother develops fever.[27–29] Placental and amniotic exposure to viruses may result in infections that can cause maternal and subsequently fetal hypoxia, which is another known risk factor for schizophrenia.[30] One or a multitude of these mechanisms may be involved in a possible association of infections with subsequent appearance of schizophrenia in offspring of mothers with COVID-19 infections.

Viruses: Influenza infection during pregnancy can be problematic and is associated with an increased risk of miscarriage and other complications for the mother and child.[31, 32] The association between the 1918–20 influenza pandemic and schizophrenia has already been discussed.[12, 15] Similar associations have been described by multiple researchers for various influenza epidemics [33] but not universally.[34] Just having a respiratory infection during the second trimester nearly doubles the risk of having a child who ultimately develops schizophrenia spectrum disorders (SSD).[35] Similarly, associations between SSD and prenatal exposure to varicella zoster, polio, and measles have been described.[36–38] Cohort studies of mothers infected with influenza viruses during pregnancy (confirmed with increased antibody titers), particularly during the first half of pregnancy, are associated with an approximately threefold increased risk of SSD in their offspring compared to controls without elevated titers.[37] Since influenza is not known
to cross the placenta [39], it has been proposed that IgG antibodies induced by influenza may traverse the placenta and cause fetal brain developmental issues via molecular mimicry.[40] Studies in pregnant animals infected with influenza reveal significant alterations in cortical volumes [41, 42], as well as altered exploratory behavior, deficits in prepulse inhibition, and decreased contact with novel objects [43], all findings consistent with schizophrenia.[44] Periconceptional genital and reproductive structure infections documented in obstetric records were associated with a fivefold increased risk of schizophrenia in offspring.[45] Moreover, elevated IgG antibodies generated in response to herpes simplex type 2 viruses in mothers were found to give rise to adults with psychosis, although the relationship was statistically insignificant after adjusting for potential covariants (odds ratio [OR] 1.22 [95% confidence interval (CI) 0.93–1.60]; \( P=0.14 \)).[46] There was no relationship between Chlamydia trachomatis infection during pregnancy and subsequent schizophrenia in the offspring, suggesting that infection per se is not sufficient and something specific may happen with infections that increase schizophrenia risk in offspring.[46]

**Toxoplasma gondii**:  *T. gondii* is a protozoan with global distribution that must complete its life cycle in cats (i.e., cellular mating must occur in cats).[47] While it is not a virus, it is the best studied infection during pregnancy that may contribute to subsequent schizophrenia in offspring. The parasite is shed as dormant microcysts in the feces of cats and is encountered by prey mice or other mammals or birds, who may ingest the microcysts in the process of environmental exploration. In the mice, the parasite infects the brain and alters behavior in a fashion that increases the susceptibility of the mice to be captured and consumed by cats, allowing the parasite to complete its life cycle.[47] *T. gondii* does not appear to alter the behavior of adult humans (unless they suffer from some immunodeficiency) but may impact the fetuses of infected mothers.[47] Approximately 40–70% of infected newborns who were asymptomatic at birth developed neurocognitive and neuromotor abnormalities resembling those observed in adults with schizophrenia.[48–50] The relationship between maternal infection and schizophrenia may be fairly specific, such that a relationship with bipolar illness could not be identified.[51] Most studies documented *T. gondii* exposure by measuring IgG antibody production, but it may be the antibodies themselves that cause fetal brain injury; if so, pre-pregnancy *T. gondii* infection may increase risk for schizophrenia in offspring.[50] *T. gondii* is prototypic for infections with neurotropic agents that may increase the subsequent risk for schizophrenia. Specifically, the infection appears to result in methylation of 132–186 separate genes, resulting in altered gene expression that may, directly or indirectly, impact brain development and function.[52] This includes PPP1R1B, which codes for the dopamine and cAMP-regulated phosphoprotein (DARPP-32), which may be directly linked to schizophrenia.[52]

**Role of inflammation**

A balance between pro-inflammatory and anti-inflammatory pathways during pregnancy is important for neurodevelopmental growth and synaptic pruning. Imbalance between these pathways has been recognized to contribute to the development of psychosis in the offspring.[53] One study found significantly elevated tumor necrosis factor (TNF)-\( \alpha \), interleukin (IL)-1\( \beta \), and IL-6 (pro-inflammatory cytokines) during the first half of pregnancy.[54] This study also indicated that early pregnancy (10–20 weeks) may be a sensitive period when cytokine alteration takes place, which may be related to the pathogenesis of schizophrenia. This is an important period when pyramidal neuron and interneuron proliferation and migration take place, disruption of which increases the risk of psychosis. Pro-inflammatory cytokines are found to be elevated in the blood as well as the cerebrospinal fluid (CSF) of patients with schizophrenia. IL-6 is specifically linked to both the presence and the severity of the disease.[16, 55] C-reactive protein (CRP) and IL-6 in the childhood and adolescence periods are associated with schizophrenia.[16, 56] Inflammatory complement, which plays a role in synaptic pruning, has also been found elevated in first-episode psychosis.[57, 58]

Exposure to prenatal maternal infection leads to disruptions in these vital neurodevelopmental pathways, particularly in the frontal areas and the mesocortical pathway.[13] Emergence of symptoms is often delayed until these individuals are exposed to psychosocial stressors in the peripubertal/adolescence age that require frontal cortical activity, noted as frontal cortical demand.[13, 14] The dysfunctional brain pathways now called on line with significant stressors are the dual ingredients of the “two-hit hypothesis”.[9] Infections, immunological responses, and biological stressors causing hypothalamic-pituitary-adrenal (HPA) axis activation result in elevated baseline cortisol levels and microglial activation with elaboration of inflammatory cytokines. These changes are associated with disruptions of glutamatergic and dopaminergic pathways, as well as reduced hippocampal volumes, all observed in schizophrenia.[59, 60]

Maternal immune activation is known to play a significant role in inflammation that may lead to development of schizophrenia in childhood not associated with any one pathogen. These inflammatory changes leading to abnormalities in dopaminergic, GABAergic, and glutamatergic pathways, in addition to changes in microglia and Schwann cells, along with psychosocial and environmental events, combine to lead to the development of psychosis in susceptible individuals. Susceptibility is determined by fetal and maternal
Role of COVID-19

When considering risk of developmental complications that are associated with maternal infection during pregnancy, there are several potential mechanisms. These include direct infection of brain tissue by the infectious organism; chemical mediators of infection, such as cytokines; indirect effects of cytokine production, such as fever; cross-reactivity between targets of the antibodies produced in response to the infection and neural tissues; and medications given to the mother in response to the infection, such as analgesics and anti-inflammatory drugs. For schizophrenia after SARS-CoV-2 infection, risk to the fetus could be mediated by extrauterine factors, such as fever or other elements of maternal immune activation, including cytokines and antibodies. Alternatively, there may be a direct effect of the virus. Vertical transmission to the fetus has been demonstrated in some 3% of COVID-19-infected pregnant mothers. Each of these potential mechanisms has experimental support. However, these mechanisms are not mutually exclusive and may each be associated with different risk factors or different phenotypic expression of the adult disease.

While the most common symptoms of COVID-19 are respiratory in nature, the mental health impact of COVID-19 has been a cause of concern since early in the pandemic. Up to 50% of the general population in a multitude of countries reported psychological distress and symptoms of anxiety, depression, and post-traumatic stress disorder. Alterations in the developing brain of the fetus of an infected mother can alter the process of brain development. Potential mechanisms of COVID-19 infection–related alterations in a developing brain are unknown and could be one or more of the mechanisms identified with viral or non-viral infections, including direct alteration due to the neurotropic nature of SARS-CoV-2 and indirect or secondary consequences of immune activation.

SARS-CoV-2 infection during pregnancy is associated with a wide range of potential problems. In one study, women with SARS-CoV-2 infection during pregnancy were at greater risk for preeclampsia (OR 1.33 [95% CI 1.03–1.73]), preterm delivery (OR 1.82 [95% CI 1.38–2.39]), or stillbirth (OR 2.11 [95% CI 1.14–3.90]). Similarly, among women with SARS-CoV-2 infection, more severe COVID-19 illness was associated with increased risk of Cesarean delivery (adjusted relative risk [aRR] 1.57 [95% CI 1.30–1.90]), hypertension (aRR 1.61 [95% CI 1.18–2.20]), and preterm birth (aRR 3.53 [95% CI 2.42–5.14]) compared with asymptomatic patients or mildly affected individuals. With increased risks for complications to the resulting infants when mothers acquire COVID-19 illness during pregnancy, it is not surprising that there are increases in neurodevelopmental issues in the first six months and one year of life. Specifically, when children born to mothers who had acquired the infection during the pregnancy were followed for one year, there was a greater rate of developmental disorders of speech or language, motor function, or unspecified psychological development compared to uninfected mothers. The increased risk for the children persisted even after data were adjusted for race, ethnicity, insurance status, offspring sex, maternal age, and preterm status (adjusted OR, 1.86 [95% CI, 1.03–3.36]; P=0.04).

Moreover, first-episode psychosis has been linked to COVID-19 infections in adults. Several similar presentations of first-episode psychosis were reported since the onset of the pandemic. This particular observation may be linked to methylation of PPP1R1B, which codes for the DARPP-32, a process that is generally mediated by dopamine release. This has led to the hypothesis that the SARS-CoV-2 virus has neurotropic properties and the potential to cause psychosis, either acutely, as a post-infectious manifestation, or as a neurodevelopmental pregnancy-associated risk factor.

Neurotropism of SARS-CoV-2: While there is limited direct evidence of the neurotropism of SARS-CoV-2, its structure and receptor-binding domain are similar to those of SARS-CoV, which was isolated from specimens of brain tissue from patients dying from the disease or presenting with severe central nervous system (CNS) symptoms. Examination of brain specimens from these patients revealed neuronal necrosis and glial hyperplasia. Viruses may access the CNS through either direct neuronal dissemination or hematogenous spread. SARS-CoV-2 generally enters cells through the angiotensin-converting enzyme 2 (ACE2) receptor. Thus, SARS-CoV and SARS-CoV-2 initially enter the body through the nose and reach the olfactory bulb by using ACE2 receptors to cross the olfactory epithelium. They then infiltrate the CNS by passing through the mitral cell-neuron synapse. Alternatively, they may infect astrocytes, which are ACE2-expressing glial cells, by invading astrocytic end-feet located near the BBB.

Animal studies have suggested that the brain is a target of infection for SARS-CoV in mice transgenic for human ACE2 receptors and have revealed that the virus enters mainly through the olfactory bulb, rapidly spreading through the neurons to other areas of the brain. SARS-CoV-2 is reported to be able to infect neurons when ACE2 receptors are artificially over-expressed in animal models. Expression of ACE2 receptors is increased after treatment with ACE-inhibitor medications, such as lisino-
Neuroinflammation: Neuroinflammation is a complex immune response within the nervous system that happens in response to damage, infection, or pathogens. A short-lived and early response, triggered by activation of glial and endothelial cells, is generally neuroprotective. Astrocytes, an abundant glial cell type in the CNS, play a role in regulating immune response and maintaining the BBB and are responsible for the regulation of neuroinflammation in response to pathogens.

SARS-CoV-2 has been shown to activate microglia and astrocytes, leading to a neuroinflammatory response. However, this response has also been linked to the “cytokine storm,” an unregulated immune response due to overproduction of pro-inflammatory cytokines, most importantly TNF-α, IL-1β, and IL-6. This can cause direct neuronal damage, leading to the observed neurological manifestations of COVID-19. These cytokines are also known to play a role in the pathogenesis of schizophrenia. The brain is particularly vulnerable to the cytokine storm due to “microglial priming,” a state in which microglia are more sensitive to stimuli and produce more cytokines and inflammatory mediators in the setting of chronic and sustained stimulation, affecting synaptic plasticity and neuronal survival. Several studies have found evidence of microgliosis and astrogliosis in COVID-19 patients who have died, suggesting a significant impact of neuroinflammation in the disease.

Discussion

COVID-19 is associated with neurologic and psychiatric morbidity that suggests a direct effect of the virus or secondary effect of an inflammatory process. These neuropsychiatric consequences can be seen during acute infection or as a long-term residual in adults. Vertical transmission of the virus probably occurs, and pregnancy-related adverse outcomes have been reported. Acute infections with a wide range of pathogenic organisms can adversely affect fetal development and have been associated with an increased likelihood of subsequent schizophrenia in adults born to mothers with the infection. COVID-19 may be associated with increased neuropsychiatric manifestations due to the nonspecific acute consequences of infection, such as hyperpyrexia, but in utero exposure may also cause specific abnormalities in brain development that can lead to schizophrenia or more nonspecific neurobehavioral issues in adulthood since neuron progenitors that express the ACE2 receptor are localized to specific brain structures, such as the hippocampus, and migrate to schizophrenia-specific pathophysiologically important areas, such as the prefrontal cortex.

The balance between inflammatory and anti-inflammatory pathways plays an important role in intrauterine neurodevelopment, especially early in pregnancy. There is evidence that dysregulation of these pathways during this critical developmental period may contribute to the pathogenesis of schizophrenia later in life by disrupting pyramidal neuron and interneuron proliferation and migration. In particular, elevated levels of TNF-α, IL-1β, and IL-6 have been implicated. These inflammatory processes may lead to abnormalities in dopaminergic, GABAergic, and glutamatergic pathway development in addition to changes in microglia and Schwann cell function. COVID-19 is associated with neuroinflammatory dysregulation through a “cytokine storm,” which elevates the same cytokines that have been implicated in schizophrenia (TNF-α, IL-1β, and IL-6).
While unfortunate, this presents us with a unique opportunity to test the inflammatory hypothesis of schizophrenia. This hypothesis can be directly tested. First, one would need to identify a cohort of patients who had been exposed to the SARS-CoV-2 virus during their pregnancy, whose offspring would be followed into adolescence and early adulthood. Exposure to the virus would be confirmed using polymerase chain reaction assays for SARS-CoV-2 in plasma samples obtained during pregnancy. [109] Documentation would include the gestational age at time of exposure. A minimum of three groups would need to be studied: (1) the offspring of women who became infected with SARS-CoV-2 during pregnancy, (2) the offspring of women who have never been infected with SARS-CoV-2, and (3) the offspring of women who had antibodies to SARS-CoV-2 prior to pregnancy. A fourth group of women who received the vaccine during their pregnancy during their pregnancy would be informative but is unlikely to be identified.[110] Cytokine measurements would be obtained regularly by the pregnant mothers throughout their pregnancies and by the offspring throughout their childhood and into adulthood. All groups would share demographics, socioeconomic background, and geographic locale. The three groups would allow for clarity in determining whether it is the active infection that is related to neuropsychiatric anomalies or the body’s response to the infection.

Such data can be supplemented with animal model studies, in which mice or rats would be infected with SARS-CoV-2 when neurons are developing and migrating in the brain (i.e., the equivalent of the human second trimester).

While clearly difficult and expensive, collection of prospective data is important to avoid the ambiguity of having purely associational data without any insight into possible mechanisms, as is the case with influenza and other respiratory viruses.

Conclusions

The COVID-19 pandemic is likely associated with a range of future neuropsychiatric consequences in people whose mothers suffered the infection during their fetal development. It is important to try to follow these offspring to determine the full range of consequences of COVID-19 infection.

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