Impact of SARS-CoV-2 Infection on Pediatric Neurological Function

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Abstract

At the tail-end of 2019 a new and lesser known strain of coronavirus (SARS-CoV-2) began to spread rapidly across China and Europe. The disease had been termed COVID-19, and in March 2020 the World Health Organization announced that we would be facing a global pandemic. Without having much preparation for this unexpected virus that had taken the world by storm, it has led to millions of infections and deaths across the globe. We are three years out from the announcement of the pandemic and researchers seem to be constantly uncovering more formidably alarming information surrounding the possible long-term consequences of SARS-CoV-2 infection. Scientists have been learning more about post-viral syndromes and illnesses in the past few decades and have been searching for treatments to sicknesses like myalgic encephalomyelitis, Epstein Barr virus, and Guillain-Barre syndrome. Similar to those afflictions, a significant number of adults who experienced COVID-19 have complained about post-viral illness and symptoms that impair their daily functioning; We are currently referring to this phenomenon as Long COVID (LC). With so many pieces of the puzzle still missing in terms of predicting long-term health outcomes following COVID-19 infection (especially in cases of repeated infection), we are left to wonder how this virus may affect the development of our youth. In this paper I will examine the impact of SARS-CoV-2 infection on pediatric neurological function. Specifically, I will review the neurological consequences from infection in utero to toddler age, effects on the brain and nervous system in adolescents, and general post-infection symptoms and illness in minors.

Keywords: coronavirus, COVID-19, pediatric, neuropsychology, post-viral illness

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Toward the end of 2019 a strain of coronavirus, SARS-CoV-2, began to spread rapidly across the human population of China and Europe, and the disease form was soon termed COVID-19. In March 2020, the World Health Organization announced that COVID-19 had evolved into a pandemic. As per the National Institutes of Health (2023) the elderly, immunocompromised, historically marginalized, and socially vulnerable groups have been determined as the categories of people with highest risk of being infected with SARS-CoV-2 and developing a severe case of COVID-19. An infection will typically be categorized under one of five titles by healthcare professionals and researchers: either asymptomatic/presymptomatic, mild illness, moderate illness, severe illness, or critical illness. Characteristic symptoms of COVID-19 include but are not limited to: cough, sore throat, loss of taste and/or smell, headache, fever, and muscle pain. As we are only about three years out from the onset of the pandemic, there is still new research emerging surrounding the ramifications of SARS-CoV-2 infection and the post-infectious syndromes some patients have gone on to develop. Since the majority of the research conducted is geared toward the adult population, we are often left to wonder: Will our youth still have the chance to grow healthy and reach appropriate developmental milestones if they have been exposed to SARS-CoV-2?

Neurological Consequences from Utero to Toddler Age Infection

It is crucial for public health to better understand how exposure to SARS-CoV-2 exposure in utero can affect a mother's offspring, and if we can anticipate any differences in the infant's development in relation to the infection. Since "studies of maternal and placental immune response suggest sex-specific responses to SARS-CoV-2 infection, with upregulation of placental interferon signaling and reduced maternal anti-SARS-CoV-2 antibodies among male

compared with female offspring" (Edlow et al., 2023), it was essential for researchers to further explore the longitudinal results of male and female infants' development following utero infection compared to offspring who had not been infected.

As a foundational study, Edlow et al. (2022) gathered electronic health records to compare the statistical risk of neurodevelopmental effects in offspring from mothers who were infected with SARS-CoV-2 versus those who were not infected. They found that of the offspring who were exposed to the virus in utero, a little over 6% were diagnosed with a neurodevelopmental disorder within 12 months of birth. In contrast, of the sample that was not exposed, only 3% received a neurodevelopmental diagnosis within the same time period. A limitation of this study is that disorders such as autism are not typically diagnosed as early as 12 months, therefore this study cannot fully account for the most common neurodevelopmental disorders. This implies that the rate of diagnosis among the exposed cohort could actually climb higher as they age. In their following research that looked to examine sex differences as an additional factor, Edlow et al. were also able to follow up with infants at the 18-month mark.

Further research conducted by Edlow and colleagues in 2023 looked to investigate the neurodevelopmental consequences of infants who were exposed to SARS-CoV-2 in the womb, and if the outcomes differed by the sex of the infant. They found that male infants at 12 months old experienced a greater risk of developing a neurodevelopmental disorder, and female infants exposed to the virus in utero did not carry the same risk as males. In statistical models that accounted for external variables such as race, healthcare accessibility, the mother's age, etc., there was a statistically significant risk of a neurodevelopmental diagnosis in male infants following a SARS-CoV-2 infection in utero, and this risk percentage only climbed higher at 18 months old. However, the study failed to include how early or far along the mothers were in their

pregnancy when infected with SARS-CoV-2; Additional studies looking to replicate this research should aim to expand and create categories for the gestational age at the time of infection, along with follow-ups of the offspring at older ages (i.e. 2-5 years old).

To better comprehend how SARS-CoV-2 infection can impact the brains and nervous systems of the younger population, we need to employ neuroimaging techniques to gather more information on what precisely is happening to them internally. In a multinational collaboration, Lindan et al. (2021) conducted the largest study to record neuroimaging in previously healthy children who went on to experience effects from SARS-CoV-2 infections. They were able to identify abnormalities in children's brains, nerves, and spinal cords associated with the virus. One of their patients, a 1-year-old boy, had been diagnosed with acute COVID-19. His neuroimaging demonstrated "confluent areas of high signal in the subcortical white matter on coronal FLAIR [fluid-attenuated inversion recovery] imaging and reduced diffusion on DWI [diffusion weighted imaging] trace". That same 1-year-old's scan displayed a pattern akin to that of ADEM [acute disseminated encephalomyelitis and "had T2 signal changes in the splenium of the corpus callosum…" (Lindan et al., 2021). According to the National Institute of Neurological Disorders and Stroke, ADEM is characterized as a neurological disorder that causes short but global inflammation in the brain and spinal cord (2023); This swelling and inflammation leads to damage of myelin, which is a protective layer encasing the axon sheath that helps neurons send electrical signals (Zillmer et al., 2008).

Similar to the previous study, researchers such as LaRovere et al. (2021) aimed to document and study the severity of neurologic involvement in children in relation to their SARS-CoV-2 infection. They recorded a case of a previously healthy toddler who after infection displayed MIS-C (multisystem inflammatory syndrome in children) and showed symptoms such

as rash, vomiting, and grand mal seizure among others. In his neuroimaging, he was categorized under an encephalitis diagnosis and his patterns are described as "diffuse T2 hyperintensity, leptomeningeal enhancement, and reduce diffusivity within the bilateral frontal lobes, basal ganglia, and thalami" (LaRovere et al., 2021) In addition, researchers had also documented one previously healthy male infant infected with COVID-19 who began to suffer from status epilepticus which led to a cardiac arrest; Imaging afterward indicated a global cerebral edema (LaRovere et al., 2021). Although every study has its limitations, the medical brain imaging used by Lindan et al. (2021) and LaRovere et al. (2021) and their results further pushes the notion that fetuses, infants, and toddlers being infected with SARS-CoV-2 can prove to have dangerous consequences, even if they were previously deemed to be healthy. However, researchers still need extended time to explore exactly how long, on average, these consequences can or will last among developing children.

Effects on the Brain and Nervous System in Adolescents

Since children's brains and bodies are growing at a rapid rate and are constantly in a state of adaptation, it is essential to determine if a SARS-CoV-2 infection can lead to obstacles, complications, or disorder within that development. Aubart et al. (2022) published a study of 19 children infected by SARS-CoV-2 who subsequently went on to develop CNS inflammatory disease related to the infection. Of the sample, 14 patients had abnormal brain MRIs showing conditions such as cytotoxic lesions of the corpus callosum (CLOCC), ADEM with brain lesions, and inflammation of the cerebellum. 74% of the sample presented with abnormal brain MRIs and cerebrospinal fluid (CSF) also proved to be abnormal in upward of half the sample (58%). The CNS involvement within the sample primarily consisted of demyelinating disorders, MOGAD, white matter lesions, ADEM, cerebellum inflammation, CLOCCs, facial neuritis, and myelitis

(Aubart et al., 2022). MOGAD is a type of autoimmune, demyelinating disorder and Aubart et al.'s "case series confirms that the onset of MOGAD can be triggered by SARS-CoV-2 infection…" (2022). The majority of patients received an anti-inflammatory treatment, and although the children of this study endured what many would consider extreme neurologic involvement post-infection, they all reached long-term recovery without report of a relapse to date. Given the severe cases documented in this study, the treatment outcomes for these patients stand as a testament to the strength of children's neuroplasticity and as an optimistic takeaway for the future of pediatric SARS-CoV-2 infections.

It is essential to evaluate how a virus like SARS-Cov-2 can affect a population that had previously been deemed as healthy, as that can aid in making the results more generalizable to the public. LaRovere et al. (2021) conducted a study that examined previously healthy adolescents who visited the hospital for a COVID-19 infection or for a multisystem inflammatory syndrome in children (MIS-C). MIS-C is assumed to be a post-infectious condition that causes severe illness and inflammation and it is associated with COVID-19 (LaRovere et al., 2021). Their study displays multiple neuroimaging of adolescent patients with extreme neurological issues associated with COVID-19 including but not limited to: meningoencephalitis, acute arterial ischemic stroke, acute hemorrhagic stroke, and severe encephalopathy. Interestingly, the researchers found seizures to be more common in children younger than 5-years-old, and anosmia/ageusia more common in patients ages 13-20. LaRovere et al. encountered 5 patients that demonstrated "severe encephalopathy, focal neurologic deficits, and visual hallucinations" (2021). They found that among the MRI scans of children who developed severe encephalopathy, there was diffusion restriction in multiple white matter areas (periventricular, deep white) alongside the corpus callosum. Similar to the neuroimaging found

in the studies mentioned earlier [Lindan et al., 2021] regarding the infants and toddlers who had been infected with SARS-CoV-2, the children in this study also displayed in their scans "…diffuse abnormal T2 hyperintensities and reduced diffusivity involving the white matter and genu or splenium of the corpus callosum…" (LaRovere et al., 2021). Out of 79% participants who reported no underlying conditions, 22% experienced neurologic involvement and 12% experienced *life-threatening* neurologic involvement related to COVID-19. This research helps to fill in some of the missing pieces regarding the patterns that manifest among adolescents who undergo severe complications from COVID-19 infection.

Approaching COVID-19 exposure from a different lens, one must also consider how the chronic stress from the pandemic alone may have impacted the brain functioning of adolescents. The following study serves as an asterisk in the context of this paper, as it is not related to effects of SARS-CoV-infection but from general societal exposure. Gotlib and colleagues discovered that adolescents suffered neuroanatomical changes and brain maturation post-pandemic shutdowns as compared to pre-pandemic (2022). The participants' brain structures developed akin to those who have suffered serious early life adversity. Their neuroimaging displays the brain structure of individuals that are older than their actual age, implying that the stress of the pandemic led to premature neuroanatomical aging. The subjects' brain scans indicated reduced bilateral cortical thickness and larger bilateral hippocampal and amygdala volume, which is a similar pattern seen in adolescents who have experienced childhood trauma (Gotlib et al., 2022). Given that the sample showcased in this study was taken from a privileged demographic, we can infer that the brain structure of adolescents living in less privileged conditions may have experienced more severe premature aging than the initial sample, although further analysis studies would be needed to confirm this inference.

Post-Infection Symptoms and Illness

As there are a limited amount of reports on the prolonged neurological manifestations in children who have been infected with SARS-CoV-2, the following study sought to establish what the primary neurological symptoms for children look like post-infection. Sener found that the top symptoms reported by adolescents during follow-up appointments were headache, seizure, and anosmia/hyposmia (2022). In addition, it was discovered that there was a significant difference between boys and girls in regards to anosmia/hyposmia, with girls being more likely to experience the loss of smell compared to their counterparts. According to Sener, it was more common among the younger age groups to experience involvement of the olfactory system (2022). In the small amount of studies that have been conducted in this area, they have demonstrated that the long-term neurological effects of COVID-19 in children manifest as "…insomnia, fatigue, muscle and joint pain, muscle weakness, dizziness, concentration difficulties, headache, sleep and appetite disturbances, irritability and inattention being among the most notable effects" (Sener, 2022). However, it should be noted that "long-term" is being defined as the 6-month follow-up visit at this point.

It is fundamental to recognize the limitation of studying post-COVID-19 effects and illness given how recent the pandemic was. Due to this, conditions such as "long-covid-syndrome" and the like have yet to be structurally and clearly defined. In an attempt to begin to close the gap in research surrounding post-infectious symptoms related to COVID-19 in children, Funk et al. (2022) looked for reported post-COVID-19 conditions (PCCs) among the younger population and observed which symptoms appeared most prominent. They found that SARS-CoV-2 infection among children aged approximately 3-10 years old was positively correlated with reporting PCCs at the 90-day mark following a hospital visit. Respiratory

(difficulty breathing, coughing, etc.) and systemic symptoms (weakness, fever, fatigue etc.) were the most commonly reported PCCs, with fatigue being the most individually reported. Additionally, there was an association found among those who experienced 5 or more symptoms during their illness to PCCs (Funk et al., 2022). It is also noted that anosmia was a top symptom for children in a similar large UK study. An inevitable limitation of this report is that researchers found that older age was associated with higher reporting level, which can imply that less-verbal and younger children are less likely or unable to report their symptoms as much, if at all.

When studying the impact of SARS-CoV-2 infection on both children and adults, we must account for the intersections of patients' identities and how it can affect their likelihood of developing a more severe case or prove to be more vulnerable to infection. Researchers Merzon et al. (2022) looked to examine the socioeconomic factors and demographic components associated with the diagnosis of Long COVID Syndrome (LCS) in a youth population. The researchers point out how LCS would be considered the "third phase" of disease in COVID-19 and offer the following explanation for this mysterious, emergent, and ongoing illness: "proposed mechanisms…include ongoing sequelae of acutely damaged tissues…continued tissue damage by persistent infection, continued sequelae of immune dysregulation, and the onset of autoimmunity" (Merzon et al., 2022). In this study, however, Merzon et al. specifically searched to find a possible correlation between LCS and a prior diagnosis of ADHD. They discovered that there is in fact a significant association between ADHD and LCS within children; ADHD is correlated with higher rates of SARS-CoV-2 infection and more severe symptoms (Merzon et al., 2022). In addition, it was found that schizophrenia was also correlated with LCS. This proves to be an intriguing link and warrants more research as both ADHD and schizophrenia can involve neuroinflammatory manifestations, not unlike LCS.

A synonym not as widely known for Long COVID Syndrome is be post-acute sequalae of SARS-CoV-2 infection, otherwise known as PASC. According to Younger (2021) the "NIH operationally defines PASC at the failure to recover from acute COVID-19, or those persistently symptomatic for > 30 days form onset of infection, with any pattern of tissue injury that remains evolving including the nervous system". Younger (2021) honed in on a case study of a 12-year old girl who was infected with SARS-CoV-2 and displayed PNS, ANS, and CNS involvement as a result; She was ultimately diagnosed with PASC. The patient in this study was bedbound 4-months after her onset of infection and seemed to continually worsen by the 6-month mark. Some of her symptoms included weakness, mild delirium, burning pain, cognitive impairment, etc. When given an Energy Dispersive X-Ray Analysis (EDX), the patient's imaging exhibited "mixed chronic distal demyelinating and axonal changes" (Younger, 2021). D.S. Younger argues there are multiple reasons to believe that PASC can often lead to an autoimmune presentation and/or condition, and references this case study as an example.

Children who have suffered from acute/subacute COVID-19 or MIS-C in relation to COVID-19 need to be monitored if they still are not feeling improvement in their symptoms or new symptoms weeks after initial infection. Researchers mentioned earlier [Lindan et al.] whom participated in an international collaboration, recorded the largest study that documents the symptoms, illness, and neuroimaging among children following SARS-CoV-2 infection to be put out thus far (2021). Lindan and colleagues were able to identify significant differences in children's brains, nerves and spinal cords following the viral infection. They separated 38 cases into four categories based on infection type (acute, asymptomatic, MIS-C, or unspecified). The most common imaging patterns among patients across the board was "post infectious immune-mediated acute disseminated encephalomyelitis-like changes of the brain, myelitis, and neural

enhancement" (Lindan et al., 2021). Category 1, which was comprised of acute COVID-19 cases, was most strongly comparable to autoimmune disease manifestations for at least half of the patients. Among the third category, which consisted of those diagnosed with MIS-C, splenial lesions and myositis were most common as compared to the children in other categories. The researchers also display in their study how dangerous developing a co-infection can be among the pediatric population when already infected with COVID-19. Since the virus creates "a breakdown of the blood-cerebrospinal fluid barrier", children naturally become more susceptible to co-infection (Lindan et al., 2021). Within their study, 4 patients (all initially grouped in category 1) had developed co-infections and all died as a result of the additional attack on their bodies and their already weakened immune systems. Given these results, we should move forward with heightened caution to ensure that a child is protected at fullest extent from catching any other viral illnesses when infected with COVID-19 and following infection.

Although the research in this area is currently in short supply, we know from what has been recently studied that pediatric SARS-CoV-2 infection and exposure to COVID-19 can increase the diagnostic risk of neurodevelopmental conditions and/or lead to significant adverse neurological symptoms and disorders, ranging anywhere from mild to severe. These changes can manifest as cognitive impairment, fatigue, stroke, multisystem inflammation, demyelination, and delirium, among others. Infection of SARS-CoV-2 in utero all the way up to teenage years can cause prolonged adverse effects in neurological functioning and behavior. It is possible that the plasticity of children's brains could serve as a protective factor when battling infection and the potential long-term repercussions, however these speculations remain unproven. Research is currently limited due to the recentness of the virus and the pandemic as a whole. Studies are

increasing, ongoing, but the possible 5-, 10-, and 20-year consequences of SARS-CoV-2 infection within the pediatric population remains to be seen.

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