Emerging Knowledge of the Neurobiology of COVID-19

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KEYWORDS

- COVID-19 • SARS-CoV-2 • Neurobiology • Delirium • Long COVID
- Neuropsychiatry

KEY POINTS

- COVID-19 causes a wide range of neuropsychiatric complications in both the acute and postacute phases.
- Acute neuropsychiatric complications are likely due to factors such as systemic inflammation and parainfectious immune mechanisms as opposed to direct viral neurotropism.
- Prolonged neuropsychiatric symptoms may result as sequalae from severe (hospitalized) COVID-19 illness.
- As well as this, debilitating neuropsychiatric symptoms may arise in relatively minor (nonhospitalized) COVID-19 cases.
- Studies on the *in utero* effects of SARS-CoV-2 infection are urgently required in order to qualify or refute a potential predisposition that a minority of children of infected mothers may have for increased risk of neurodevelopmental and neuropsychiatric disorders.

INTRODUCTION

COVID-19, the syndrome caused by infection with the novel coronavirus SARS-CoV-2, has, at the time of writing, affected more than 200 million people worldwide.[1] In mild COVID-19 illnesses, which constitute the large majority, viral replication tends to be confined to the upper respiratory tract, although in severe cases COVID-19 may affect

multiple organs, including the central nervous system.[2] Indeed, high rates of neuropsychiatric complications in COVID-19 were expected based on data from previous coronavirus epidemics.[3]

Large studies have indicated high rates of neurologic and neuropsychiatric complications of COVID-19, which in the majority are nonspecific and include fatigue, myalgia, depression, anxiety, and headache.[4] As well as these common neuropsychiatric complications, there are rarer central nervous system complications, such as encephalitis and, possibly, psychosis.[5,6] In the acute phase of COVID-19, delirium is the most common neuropsychiatric manifestation and is thought to arise secondary to the inflammatory response to SARS-CoV-2 replication.[7] Furthermore, cerebral vasculopathy secondary to the inflammatory response likely predisposes to complications ranging from acute infarctions (ie, stroke) to subtle microvascular alterations.[8]

Toward the beginning of the pandemic it was hypothesized that SARS-CoV-2 may be neurotropic: that is, able to directly invade and replicate inside neuronal cells.[9] The scientific community had good reason to suspect this, as SARS-CoV-2 was found to enter human host cells via the angiotensin-converting enzyme 2, a transmembrane protein expressed by multiple tissue types across the body, including in the nasal neuroepithelium, where it is found in high levels.[10] Many patients with acute COVID-19 were found to experience anosmia, which in some cases is long-lasting, suggesting possible viral interference with the olfactory neurons, which may have represented a possible route of entry into the proximal central nervous system.[11] This hypothesis has been supported by preclinical data, which have suggested that the virus is able to replicate inside laboratory simulations of central nervous system tissue, such as brain organoids,[12] as well as suggestions from some neuroimaging data.[13] There are, however, limits to the conclusions that can be drawn from these in vitro studies, and there has been very scant evidence of neurotropism from clinical and postmortem studies.[9]

Over the roughly 18 months of the pandemic, the neurotropic hypothesis has gradually fallen out of favor, and there have been other, more nuanced, neurobiological hypotheses posited to explain the high rates of neuropsychiatric complications of COVID-19.[9] Many of these hypotheses implicate the immune response to the virus, which is likely to be responsible for many of the acute neuropsychiatric complications of the disorder but is also a potential contributing factor to longer term neuropsychiatric sequelae of COVID-19, many of which are currently known as "long COVID."[14] Indeed, large numbers of patients with long COVID symptoms, ranging from persistent anosmia, to neurocognitive abnormalities, to persistent and disabling fatigue, will continue to suffer as a longer term result of the pandemic.[2,14]

What follows is a broad discussion of the current neurobiological hypotheses on the cause and pathophysiology of both the acute and longer-term neuropsychiatric complications of COVID-19. These mechanistic factors are discussed in relation to the commonest neuropsychiatric syndromes that arise in the context of COVID-19.

DISCUSSION
What are the Mechanisms Behind Acute Neuropsychiatric Complications of COVID-19?

Delirium
Delirium is a syndrome defined as an acute disturbance in attention and awareness, as well as impairment in other aspects of cognition such as memory or perception, which tends to fluctuate in severity over days or hours. In this article the authors use delirium as the default term for such patients, reserving the term acute encephalopathy for clinical syndromes that incorporate rapidly developing pathobiological brain processes

with additional neurologic signs or symptoms (for a consensus recommendation on this issue please see Ref.[15]).

Delirium is common, and the incidence in elderly hospital inpatients has been estimated to be up to 35%.[16] Although the cause is often multifactorial, it is well established that infections and the resultant systemic inflammatory response may lead to delirium in predisposed individuals, perhaps through cytokine-induced cholinergic neurotransmitter deficiencies.[17] Data have indicated that many patients with COVID-19 experience delirium in the acute phase—in some populations up to half of all cases—and in some delirium can be the sole presenting feature.[18] There is evidence demonstrating a higher prevalence of delirium in those with severe infection,[19] especially in those admitted to intensive care (ICU)[20] and in the elderly or those with dementia.[7] Despite this, delirium in COVID-19 has also affected those without typical risk factors, including younger patients.[21]

Some authors have suggested that patients with COVID-19 may be at risk of a dysfunctional immune response mediated by massive cytokine release, known as a "cytokine storm."[22] Massive cytokine release is postulated as being responsible for multiorgan pathology in severe COVID-19, for example, acute respiratory distress syndrome. Some patients have shown cytokine storm immune responses to other epidemic viruses, such as H1N1 influenza[23] and other coronaviruses.[24] Despite the theoretic risk of a cytokine storm, the data have not been consistently supportive of its common presence in COVID-19.[25] Whether or not patients with COVID-19 experience cytokine storms, high levels of circulating inflammatory markers, as is seen in any immune response to an infectious pathogen, may lead to central nervous system complications such as delirium.

Patients with COVID-19 have also been shown to have high levels of circulating serum cytokines, such as interferon-gamma (IFN-γ) and interleukin-17 (IL-17), which suggest a proinflammatory T-helper type I (Th1) and Th17 immune response.[26] Proinflammatory cytokines, such as IL-6, IL-8, and tumor necrosis factor alpha, seen in severe COVID-19,[27] can interfere with blood-brain barrier (BBB) permeability via upregulation of cyclooxygenase-2 and activation of matrix metalloproteases.[28] This COVID-19–related BBB breakdown has been shown in both preclinical[29] and clinical research.[30] Disruption of the BBB may facilitate entry of inflammatory or immune mediators, which induce or mediate neuroinflammation via microglial activation and T-cell invasion.[31] If severe enough, this may lead to lasting neuronal damage and subsequent cognitive impairment.[32]

Affective disorders

Depression has been reported at high levels in patients with acute COVID-19, although most studies to date have used basic screening tools in hospitalized patients, both of which are factors that may misrepresent true overall prevalence.[33] There are, of course, many reasons why a person with a severe respiratory pandemic illness may develop low mood or depression beyond the neurobiological effects of the infection. Nevertheless, it is possible that COVID-19 itself may directly lead to symptoms of depression, particularly as the risk of depressive symptoms may be increased with more severe COVID-19 illness.[34] The most plausible method of neurobiological depressogenesis in response to COVID-19 is via the (1) inflammatory response or (2) as a result of cerebrovascular damage secondary to systemic endotheliopathy, poststroke depression, or hypoxic brain injury.

Inflammatory cytokines have been postulated to cause depressive symptoms for decades,[35] and one evolutionary model of depression suggests that social withdrawal and "forced rest," both symptoms that overlap with those seen in depression, are a

useful adaptive response to an infection or injury.[36] There has been evidence to support the hypothesis: chronic inflammatory conditions such as rheumatoid arthritis are associated with high levels of depression,[37] and administration of proinflammatory cytokines (eg, IFN-α–based immunotherapy in chronic hepatitis C) can induce depressive symptoms in humans and animals.[38] Some data have suggested that the degree of inflammation in COVID-19 is correlated with the extent of depressive symptoms,[39] although this has not always been replicated.[40] It remains to be established whether cytokines play a causal role in depressive illness in COVID-19 and other inflammatory conditions or whether they simply represent epiphenomena without major significance (or, more likely, that the bidirectional relationship is complicated and not yet fully understood).

As has been noted, patients with COVID-19 are predisposed to cerebrovascular pathology, including acute stroke.[8] It is well known that the incidence of depression is high following stroke.[41] In addition, multiple neuroimaging studies in patients with COVID-19 (typically severe cases) have consistently shown structural brain lesions, particularly in white matter tracts.[42] It is possible that this structural damage predisposes individuals to a depression in which vascular or structural changes are a contributing factor: a "vascular depression." The vascular depression hypothesis posits that cerebrovascular damage, or vascular insufficiency, leads to disruption in cerebral functioning, especially of frontostriatal circuits, which predispose to low mood.[43]

In addition, it was noted in previous coronavirus epidemics that cases of acute affective disorders, including mania, arose in the context of systemically administered corticosteroid (eg, dexamethasone, prednisolone) therapy.[3] Following large randomized controlled trials that supported their use, corticosteroids are now routinely prescribed to hospitalized patients with COVID-19.[44] Corticosteroids are known to cause a spectrum of neuropsychiatric side effects, including acute mania and depression, which occur in an estimated 6% of prescriptions.[45] The mechanisms by which steroids induce affective symptoms remain unclear, although disruptions to the hypothalamic-pituitary-adrenal axis are commonly seen in depression,[46] and it is hypothesized that glucocorticoids may cause altered neurotransmitter and neuroreceptor gene transcription.[47] Nevertheless, despite these plausible assertions, there have only been sporadic reports of mania in hospitalized patients with COVID-19,[48] which have not been replicated in other samples.[4,49]

Psychosis

Psychosis has long been associated with viral illness, and as far back as the seventeenth century, certain respiratory infections including influenza were linked with acute psychotic disorders.[50,51] At the height of the 1918 to 1919 Spanish Influenza pandemic, hundreds of cases of postpsychotic influenza were reported.[50] In COVID-19, the incidence of psychotic disorders is estimated at around 1%, increasing to 3% for those with (ICU) admission and 7% in those with delirium.[52] The factors implicated in the genesis of psychotic symptoms in COVID-19 is likely to be multifactorial and center around physiologic and psychological stress.[6]

An additional factor for consideration is the confounding of true psychotic symptoms by the presence of delirium. Psychotic features are often present in delirium, and diagnosis of a true psychotic disorder may be difficult or even impossible in the acute illness phase. However, cases published earlier in the pandemic reported psychotic disorders in patients who have screened negative for delirium and without grossly abnormal inflammatory profiles.[48] Another important confounder may be the use of corticosteroids in treating COVID-19, which are well documented to precipitate

delirium and hallucinations.[45] In summary, despite substantial evidence for biological plausibility implicating SARS-CoV-2 in the generation of psychotic illnesses, a temporal, definitive association is far from proved, especially because potential confounders such as delirium and treatment side effects are unaccounted for.

Nevertheless, immunopsychiatric research has implicated inflammatory processes in the development of psychosis,[53] and epidemiologic studies have shown robust associations between viral infections and subsequent development of psychosis, either in childhood or via maternal infection in utero.[54,55] A small subset of psychoses are autoimmune in origin, and the development of autoantibodies to receptors has been associated with acute viral infection. Nevertheless, this represents a small subset of psychotic patients and most of the patients tested will be negative for autoantibodies.[56] Cell or antibody-mediated postinfectious psychosis is therefore a potential, albeit likely rare, mechanism for the pathogenesis of COVID-19 psychosis.

Encephalitis

Encephalitis is defined as inflammation of the brain parenchyma that occurs most often in response to pathogens, systemic inflammation, or autoimmune antibodies.[57] Encephalitis, as well as the related inflammatory syndrome of acute disseminated encephalomyelitis,[58] has been reported to occur in patients with COVID-19.[59] In order for cerebral inflammation to occur, either pathogens or inflammatory mediators (or both) must enter the central nervous system, for example, via disruptions in the BBB. Although in theory this disruption could also allow for the migration of SARS-CoV-2 into the cerebral parenchyma infection (as seen in, for example, herpes simplex encephalitis), this has not yet been borne out by most data.[9]

Instead, there are data suggesting the presence of anti-SARS-CoV-2 antibodies[30] as well as autoantibodies, such as antineuronal,[60] antiglial,[60] and anti-NDMAR antibodies[60] in the cerebrospinal fluid of patients with neurologic symptoms associated with COVID-19. High-affinity SARS-CoV-2-neutralizing antibodies have been shown to cross-react with self-antigens found in the central nervous system.[61] These findings support the possibility of autoimmune-mediated encephalitis in a tiny minority of patients with severe COVID-19, although it should be emphasized that the presence of autoantibodies alone does not necessarily imply direct pathogenicity. Nevertheless, clinical series have shown improvement in patients with COVID-19–related encephalitis treated with immunotherapy, which does suggest a role for a host immune response in some patients.[62]

Cerebrovascular pathology

Patients with COVID-19 have been found to be susceptible to cerebrovascular pathology, including acute stroke.[8] Stroke occurs in approximately 1% to 3% of hospitalized patients with COVID-19 and 6% of those admitted to ICU.[63] Stroke can result in significant neuropsychiatric complications, with around one-third of stroke survivors experiencing anxiety, depression, or apathy.[64] COVID-19–associated strokes have been suggested to be more likely to present with large vessel occlusion, multiterritory involvement, and involvement of otherwise uncommonly affected vasculature than is typically, with clinically observed neurologic deficit typically being severe.[63]

Although neuroimaging findings in COVID-19 have often been heterogenous and nonspecific,[65] gray matter lesions occur most frequently in the temporal and precentral gyrus and bilateral thalamus, whereas white matter lesions occur most frequently in the corticospinal tract and corpus callosum.[42] Changes in thalamocortical connectivity have the potential to impair regulation of arousal and consciousness[66] and therefore may be responsible for observed symptoms such as agitation, disorientation,

confusion, and loss of consciousness.[67] Corpus callosum injury impairs interhemispheric communication, potentially causing disconnection syndrome with neurocognitive deficits.[42]

Endotheliopathy (ie, a disruption of endothelial cells responsible for maintaining vascular integrity) in COVID-19 has been identified as a substantial contributor to development of thrombotic complications such as stroke.[68] Because SARS-CoV-2 particles infiltrate endothelial cells of the cerebral vasculature, there is activation of macrophages, neutrophils, complement pathways, and thrombin production; together, these encourage deposition of microthrombi.[69] Cerebral postmortem studies demonstrate acute hypoxic-ischemic injury from micro- and macroinfarcts, as well as hemorrhage and mild-to-moderate inflammation,[70] although correlation between histopathological findings and SARS-CoV-2 RNA in brain has been lacking.[71]

Patients with severe COVID-19 are at risk of hypoxic-ischemic brain injury both from the direct viral effects on pulmonary tissue, the inflammatory sepsis response (including hypotension),[72] as well as iatrogenic factors such as intubation.[73] Cerebral microhemorrhages have also been reported in cases of patients with severe COVID-19 requiring intensive care.[74] It has been suggested that these may arise secondary to hypoxia-induced cerebral vasodilatation and release of cytokines, reactive oxygen species, and vascular endothelial growth factor, as a similar pattern has been observed in individuals with non–COVID-19–related respiratory failure and critical illness.[75] Although the long-term effects of cerebral microhemorrhages in patients with COVID-19 are uncertain, in other diseases independent association has been observed between microhemorrhages and cognitive impairment and disability.[76]

What are the Mechanisms Behind the Longer Term Neuropsychiatric Complications of COVID-19?

Long COVID

Many patients who are infected with COVID-19 will experience persistent neuropsychiatric symptoms such as sleep disturbance, fatigue, cognitive difficulties, anxiety, and posttraumatic stress symptoms, depression, and myalgia.[77] Although, as yet, there is no universally agreed-on definition for this syndrome, which is thought to affect around 10% of COVID-19 survivors, it is currently most often referred to as long COVID.[14] The exact symptomology of long COVID is not yet clear with patients often reporting varied, relapsing-remitting symptoms[78] and the presence of symptoms varying depending on the methodology used to capture them as well as the populations studied.[77,79] Given the heterogeneity and unknowns that characterize current understanding of long COVID, mechanistic hypothesis remains speculative at present. Current understanding suggests at least 3 possible mechanistic hypotheses: (1) functional impairment akin to "post-ICU syndrome" (see later discussion), (2) lingering inflammation and immune dysfunction initially precipitated by the acute infection, and (3) physiologic changes induced by SARS-CoV-2, including persistence of the virus after the acute illness.[80] Regardless of the primary mechanistic pathway, symptoms in a subset of patients may be prolonged in part due to nonvolitional attentional diversion and somatic hyperawareness that arises secondary to the symptoms.

Intuitively, we might expect to see long COVID overrepresented in patients who have been hospitalized by severe acute COVID-19. Indeed, in some studies, length of hospitalization with COVID-19 has been identified as a predictor of greater impairment in functional status[81]; this indicates that prolonged symptoms that persist could in part demonstrate a broader post-ICU syndrome, a constellation of symptoms found in many patients following a critical illness, which is driven by factors such as

prolonged deconditioning and the stress of responding to a life-threatening illness.[82] The story, however, is a little more complex, and many suffer with debilitating long COVID symptoms that emerge after a relatively "mild" acute COVID-19 illness[2,77]; indeed, one study found a correlation between a weaker anti-SARS-CoV-2 response and long COVID,[83] which indicates that long COVID is likely a heterogenous illness that includes a large proportion of patients who suffer with a phenotypical distinct entity to post-ICU syndrome.[77]

One theory suggests that the neuroendocrine and inflammatory effects of infection can mediate symptoms of withdrawal and fatigue, consistent with an evolutionary perspective which emphasizes the survival benefit gained from withdrawal to convalesce from a pathogenic illness (as discussed earlier). Furthermore, the physical and psychological exhaustion from the infection may lead to deconditioning, as was seen in severe acute respiratory syndrome (SARS, a coronavirus).[3]

Initial attempts have been made to establish biomarkers that may help us understand the underlying pathophysiology of long COVID. In patients discharged from hospital, lymphopenia and elevated D-dimer and C-reactive protein levels were found in a minority.[84] This persistence of derangement in biomarkers, particularly those associated with inflammation, indicate that long COVID symptoms could be related to a lingering "tail" and an abnormal inflammatory response to an infection.[85,86]

Some investigators have suggested that long COVID symptoms may linger due to the prolonged presence of SARS-CoV-2 after the acute illness, partly as some data have indicated that SARS-CoV-2 RNA continues to be found in bodily fluids after the acute illness (particularly in stool samples) and that B-cell somatic hypermutations continue months after exposure, suggesting an ongoing and evolving immune response to a persistent virus.[87] Nevertheless, there is no consensus on this hypothesis, particularly because it has not previously been considered relevant in previous coronavirus infections, and the presence of viral RNA does not necessarily translate into clinical relevance.[88]

Overall, firm evidence for the underlying neurobiology of long COVID is unclear, and the literature lacks large-scale prospective studies. The evidence so far is mixed, indicating possible avenues for further exploration, for example, whether increased inflammation during the infective phase of COVID-19 may predispose to more severe symptoms and that those with "long COVID" may have high to normal levels of inflammatory markers that exacerbate their symptoms. These increased inflammatory markers may or may not interact with the nervous system to drive abnormalities and autonomic dysfunction that drive symptoms.[89] All of these physiologic mechanisms must be seen in the biopsychosocial context where the experience of COVID-19 infection and its psychological effects may influence lingering symptoms.

Neurocognitive syndromes

Longer term neurocognitive impairment resulting from COVID-19 is likely to occur in some patients. Indeed, data from the SARS epidemic indicated that some hospitalized patients had impairments of memory, attention, concentration, or mental processing speed at 1-year follow-up[3]; this has been replicated in several studies in COVID-19, albeit many with shorter follow-up periods.[19,90] Whether or not these cognitive abnormalities are specific to COVID-19 can be contested, as cognitive deficits following many severe illnesses requiring intensive care (intensive therapy unit) admission are well recognized.[91] Nevertheless, as with many other long COVID symptoms, data suggest that the degree of longer-term cognitive impairment is not always related to the severity of the acute COVID-19 illness.[92]

Longer term neurocognitive syndromes following acute COVID-19 are likely to be seen in 3 distinct but overlapping patient groups: (1) those with postdelirium cognitive impairment, driven by central nervous system inflammation,[39] (2) those without preceding delirium, suggesting other mechanisms of cognitive deficit such as hypoxic brain insults,[93] and (3) those with a milder course of illness with alternate mechanisms of cognitive impairment.

It is well established that delirium is a risk factor for the subsequent development of neurocognitive impairment and dementia and can precipitate a stepwise, irretrievable decline in cognition in people who already have a dementia diagnosis or with mild cognitive impairment.[94] This suggests that we may see a sharp increase in the incidence of dementia as a result of COVID-19 over the coming years.

Neurocognitive deficits postdischarge from COVID-19 illness have been associated with low blood oxygenation as well as the presence of acute respiratory distress syndrome, which may indicate hypoxic brain insults in pathogenesis of persisting cognitive deficits.[90] It is known that medial temporal brain regions (including the hippocampus, which has a key role in short-term memory) are particularly sensitive to hypoxaemia,[95] and subtle neuroimaging changes across the brain, including in the hippocampus, have been found in patients who were hospitalized with severe COVID-19.[96] Other neuroimaging studies in COVID-19 have shown areas of brain hypometabolism in many brain regions, including limbic and paralimbic areas, brainstem, and cerebellum on positron emission tomography scans. The presence of these markers of brain hypometabolism have been associated with persistent cognitive abnormalities postacute COVID-19 illness.[97]

Finally, cognitive and attentional deficits, known by some as "brain fog," is a common feature of long COVID.[98] The mechanisms whereby these subjective cognitive changes arise have yet to be fully understood and will likely be complex and multifactorial. Nevertheless, it is likely that a proportion of patients, particularly those in younger age demographics than typically affected by dementias, will have symptoms indicating functional cognitive disorder, which, as with any functional disorder, may arise from an acute physical illness such as COVID-19. Functional cognitive disorders cause distress and disability; however, they do not represent a degenerative brain disorder.[99] Similar functional cognitive symptoms have been seen in other conditions such as functional neurologic disorder, chronic fatigue syndrome/myalgic encephalomyelitis (CFS/ME), and fibromyalgia.[100]

In utero effects

COVID-19 may adversely affect neonatal outcomes, with reported higher rates of fetal distress, low birth weight, intrauterine growth restriction, and increased rates of preterm births.[101] Some have suggested that this may translate into increased risk of neurodevelopmental and neuropsychiatric disorders, although at present these hypotheses are speculative.[102] Maternal infection with other viruses (eg, herpes simplex, rubella, poliovirus, Zika, and influenza) have been associated with increased risk of neurodevelopmental disorders,[103] including, for example, autism spectrum disorder (ASD).[104] Some of the strongest evidence linking maternal viral infections with schizophrenia to date is from the 1964 rubella pandemic, in which there was a 10- to 15-fold increased risk of schizophrenia spectrum disorders in offspring born to mothers who contracted the virus.[105]

Mechanisms behind these putative effects are broadly 2-fold: either via immune constituents or maternal hormones interacting with fetal neurogenesis. Elevated levels of immunoglobulin G (IgG) and IgM, which occur in viral infections, may cross into placental circulation, leading to disruption in neuronal development.[106] As has been

noted, SARS-CoV-2 may elicit a Th17 (IL-17) immune response, and studies in mouse models show administration of IL-17 produces an autismlike phenotype and behavior in offspring.[107] Similarly, the physiologic, metabolic, and endocrine correlates of maternal physiologic stress, which may occur in the context of a viral illness, have been noted to be associated with increased risk of neurodevelopmental outcomes in offspring, including ASD[103] and schizophrenia.[108] Whether or not these factors will be relevant to the offspring of mothers who are COVID-19 positive is not yet known.[109]

SUMMARY

It has been well established that many patients with COVID-19 illness will develop neuropsychiatric complications. The neurobiology behind these acute complications is continuing to emerge, and emphasis is now placed on inflammatory and parainfectious systemic effects of COVID-19 illness as opposed to direct viral neurotropism. Beyond the COVID-19 pandemic, research into this area may help to elucidate mechanisms by which other viral illnesses may contribute to illnesses such as psychosis, cognitive impairment, and CFS/ME.

Many patients will experience long-lasting neuropsychiatric difficulties following COVID-19. These patients fall roughly into 2 distinct but overlapping groups: those who had a severe COVID-19 illness with acute neuropsychiatric complications and those with "milder" COVID-19 illnesses, who nevertheless have lasting neuropsychiatric effects. Finally, it has been speculated (although far from proved) that offspring born to mothers who had COVID-19 may be more at risk of neurodevelopmental conditions, principally autism spectrum disorder and schizophrenia spectrum disorders.

In clinical practice, patients can be reassured that it is most likely that the SARS-CoV-2 virus will not directly infect their central nervous system; however, physicians are encouraged to be alert to the common neuropsychiatric manifestations. Delirium is particularly common, and in some patients will be the sole presenting syndrome of SARS-CoV-2 infections. Finally, patients should be strongly advised to follow public health advice on COVID-19 transmission and to receive an SARS-CoV-2 vaccination whenever possible, as this is the most effective way of reducing risk of neuropsychiatric complications associated with COVID-19.

CLINICS CARE POINTS

- Patients in clinic can be reassured that it is very unlikely that the SARS-CoV-2 virus will directly infect their central nervous system.
- Nevertheless, do not forget the brain when dealing with acute COVID-19. Delirium is particularly common and in some patients will be the sole presenting syndrome of SARS-CoV-2 infections.
- Patients should be strongly advised to follow public health advice on COVID-19 transmission and to receive an SARS-CoV-2 vaccination whenever possible, as this is the most effective way of reducing risk of neuropsychiatric complications associated with COVID-19.

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