

COVID-19 and post-traumatic stress disorder: The perfect ‘storm’ for mental health (Review)

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Abstract. Since its outbreak, in December, 2019, in the Chinese city of Wuhan, coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has evolved into an ongoing global pandemic. Due to the novel antigenic properties of this virus, the world population could not develop immunity effectively and this led to the subsequent spread of COVID-19. This caused an unprecedented emergency situation with significant negative effects on health and well-being both on an individual and societal level. Apart from health, economic and social consequences, the impact of this pandemic on mental health is increasingly being reported in the scientific literature. The present review aimed to provide a comprehensive discussion of the possible neurological and neuropsychiatric manifestations of SARS-CoV-2, together with the related underlying molecular pathways. In

addition, the present review focused on populations which are at a higher risk of developing psychiatric disturbances due to the COVID-19 pandemic and discussed possible routes of clinical management and therapeutics to minimize the burden associated with psychiatric disorders. Moreover, research findings exploring the prevalence of COVID-19-related post-traumatic stress disorder (PTSD) symptoms across vulnerable groups, including children, adolescents and COVID-19 survivors are presented, with particular emphasis on those with severe disease who required hospitalization and/or intensive care unit admission. Based on the available literature, the identification of potential determinants associated with PTSD across the different populations is underlined. Lessons learnt from the pandemics across the globe together with the ongoing research on COVID-19 and its impact on mental health, highlight the utmost importance for evidence-based, proactive and targeted interventions in high-risk groups aiming to mitigate the risks and manage vulnerabilities.

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Abbreviations: COVID-19, coronavirus disease 2019; SARS, severe respiratory syndrome; SARS-CoV-1, severe respiratory syndrome coronavirus 1; SARS-CoV-2, severe respiratory syndrome coronavirus 2; PTSD, post-traumatic stress disorder; ICU, intensive care unit; DSM-5, Diagnostic and Statistical Manual of Mental Disorders; MERS-CoV, Middle East respiratory syndrome; ACE2, angiotensin converting enzyme 2; BBB, blood brain barrier; CNS, central nervous system; PTSS, post-traumatic stress symptoms; GAD, generalized anxiety disorder

Key words: COVID-19, SARS-CoV-2 neurobiology, mental health, post-traumatic stress disorder, trauma

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1. Introduction

Since late December, 2019, humanity has been facing an unprecedented situation due to the coronavirus disease 2019 (COVID-19) outbreak which began in Wuhan, China. COVID-19 is a highly contagious disease, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2),

which has evolved into an ongoing pandemic (1). The World Health Organization declared this viral infection as a public health emergency of international concern on January 31, 2020 (<https://bit.ly/2Tud4mX>) and as a pandemic on March 11, 2020 (<https://bit.ly/3qF3IRA>). Eighteen months into this unprecedented and rapidly evolving situation, according to the latest data, the pandemic has led to >195 million cases with confirmed SARS-CoV-2 infection and to >4.1 million deaths worldwide (<https://bit.ly/2TktAG1>). Despite the extensive commitment from the global biopharmaceutical industry to address COVID-19 and its rapid development, and the worldwide distribution of several vaccines with demonstrated efficacy in preventing symptomatic infections and COVID-19 related admissions to hospital and deaths (2), there is currently no available medication for the effective treatment of the disease; thus, clinical management relies on symptomatic relief, supportive care and isolation. There is, also, uncertainty as regards the long-lasting immunity and potential long-term adverse effects of the vaccines, the duration of the pandemic and the extent of the effects of the pandemic on the mental health of the world's population. Moreover, the precautionary restrictive measures taken to control the spread of the virus, ranging from social distancing to strict lockdown regulations, have created an insecure and stressful environment at all levels, health, economic and social (3). Stressful situations, such as the intense insecurity of a contagious life-threatening virus, fear of being infected or having contracted the virus, being hospitalized with less or more severe COVID-19, being admitted to an intensive care unit (ICU), the loss of a loved one, mandatory and drastic changes to everyday life with uncertain financial and future prospects, alongside insufficient coping skills and stress management strategies (4), have all contributed to posing a significant burden on the mental health of individuals (5-7). These situations and may also be perceived as traumatic events (8). Studies have suggested that health-related pandemic disasters may lead to post-traumatic stress disorder (PTSD) symptomatology (9-11), a mental health impact described as the 'second tsunami' in the SARS-CoV-2 pandemic (12). The COVID-19 pandemic is a potentially traumatic event given its characteristics (unpredictable, extreme, prolonged, based on an unknown/unfamiliar danger, posing threat of death). However, according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-5), only some individuals may meet the qualifying trauma exposure criteria for PTSD as a result of the pandemic and these are the following: Those who have themselves suffered from severe COVID-19 illness and potential death; individuals who, as family members and health care workers, have witnessed the suffering and death of others; individuals who have learned of the death or risk of death of a family member or friend due to the virus; and individuals who have experienced extreme exposure to aversive details (e.g., first responders and hospital personnel). The DSM-5 diagnosis of PTSD requires the presence of symptoms from the following four symptom clusters: Intrusion symptoms associated with traumatic event(s); persistent avoidance of stimuli associated with traumatic event(s); negative alterations in cognition and mood associated with traumatic event(s); and marked alterations in arousal and reactivity associated with traumatic event(s) commencing or

becoming more severe following the occurrence of traumatic event(s) (13).

2. Neuropsychiatric manifestations of SARS-CoV-2

An association between psychological distress and the neuropathological manifestations of the disease has already been suggested, as patients with COVID-19 have consistently been shown to exhibit significantly higher levels of anxiety, depression and stress-related disorders when compared with non-COVID-19 subjects (14). Indeed, apart from the prominent respiratory symptoms, SARS-CoV-2 has been shown to induce neurological and neuropsychiatric manifestations that vary both in intensity and duration; neurological symptoms include headaches, dizziness, hyposmia or anosmia, ageusia, ataxia, seizures, encephalitis, encephalopathy, sensory impairment, cranial neuropathies, acute cerebrovascular disease, para-infectious peripheral nerve-related disorders, such as Guillain-Barré and Miller Fisher syndromes, and in certain cases, neuronal autoimmunity (15,16). Neuropsychiatric symptoms include cognitive decline, confusion, delirium, dementia, insomnia, anxiety, depression and psychotic spectrum disorders (17-19).

Viral neurotropism has already been documented for coronaviruses SARS-CoV-1 and Middle East respiratory syndrome (MERS-CoV). However, there is no sufficient evidence to also support the neuro-invasive potential of SARS-CoV-2 (16,19,20); most arguably, the virus interacts with the angiotensin converting enzyme 2 (ACE2) receptor on host cells to facilitate entry. Neural cells expressing ACE2 are found in circumventricular organs that are involved in cardiovascular and respiratory regulation, and have little or no protection of the blood brain barrier (BBB), thus representing central nervous system (CNS) sites that are quite vulnerable to viral infection (18). Clinical presentations of PTSD, depression, pain disorder, panic disorder and obsessive-compulsive disorder in survivors with SARS-CoV-1 have been shown to be markedly increased at 31-50 months post-infection, as compared with their prevalence pre-infection (19,21). Similarly, patients with COVID-19 have been found to present with a significantly higher incidence of an altered mental status, mood disorders, insomnia, anxiety and dementia, while the risk of developing a post-infectious psychiatric disorder appears to be ~2-fold higher when compared with pre-infection rates (22-24). In individuals with a predisposition to stress-related disorders or with pre-existing neuropsychiatric conditions, SARS-CoV-2 can accelerate the development of significant psychiatric disorders, with significant implications for optimal medical and psychiatric care (14,18).

Even though the exact mechanisms of COVID-19-associated neuropsychiatric symptoms are not well known, neurotropic activity manifests as a viral infection of the nervous tissue and has been postulated to occur via two possible pathways: i) A hematogenous route, which may include the infection of BBB endothelial cells, infection of the blood-cerebrospinal fluid barrier epithelial cells, or via myeloid cell trafficking, a process that essentially utilizes inflammatory cells as Trojan horses to gain access to the CNS; ii) a neuronal transport route which uses retrograde axonal transport through the olfactory, the respiratory and the enteric nervous system (15,25). CNS invasion

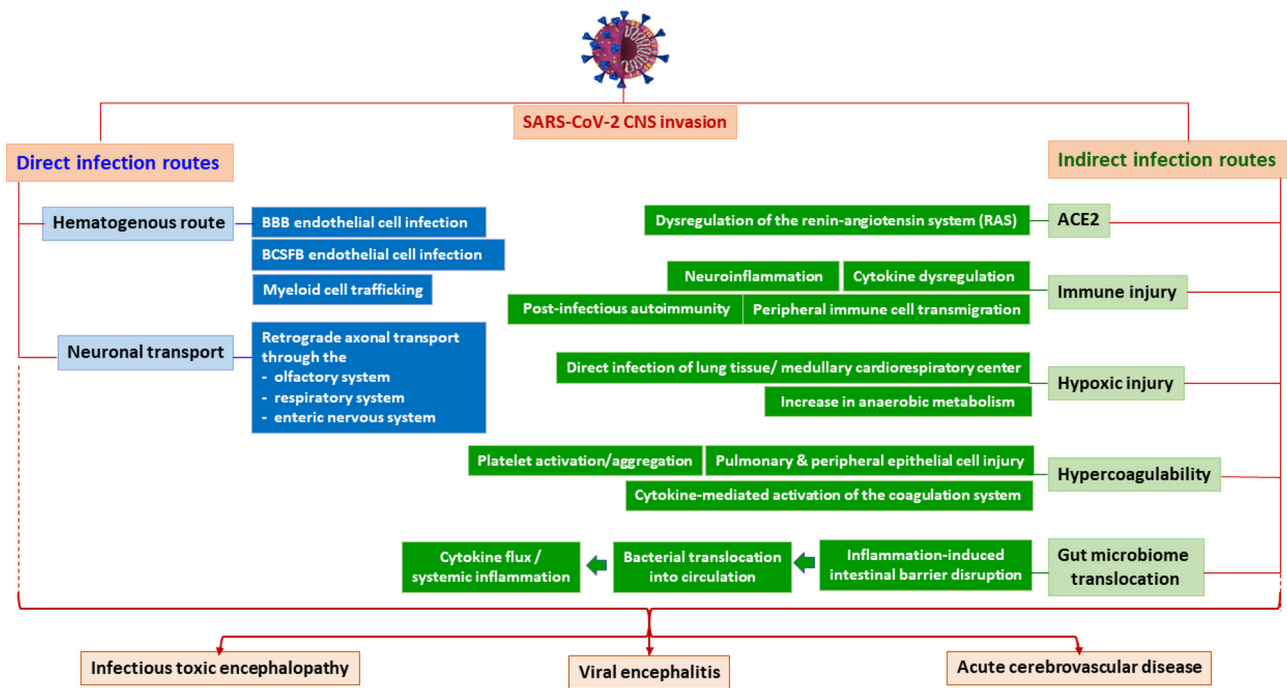


Figure 1. Postulated pathways for SARS-CoV-2 CNS invasion. SARS-CoV-2 can use both direct and indirect pathways to invade the brain. BBB, blood-brain barrier; BCSFB, blood-cerebrospinal fluid barrier; ACE2, angiotensin converting enzyme 2. The figure was adapted from the study by Rege (25).

may also occur via deregulated inflammatory responses, such as cytokine dysregulation and neuroinflammation, which may increase BBB permeability, thereby facilitating viral entry, or as a secondary effect of other organ system failure, such as cardiorespiratory failure, or secondary to the embolic process triggered by SARS-CoV-2 (15,18,25). Furthermore, as certain anti-viral drugs, including chloroquine, have already been shown to cause CNS-related adverse events, both neurological and neuropsychiatric, it is possible that, in the context of COVID-19, such treatments may contribute towards increasing neuronal stress and neuroinflammation, ultimately causing neuronal damage that is associated with neuropsychiatric disturbances (14,26). A more-detailed overview of the direct and indirect pathways of SARS-CoV-2 CNS invasion is illustrated in Fig. 1.

3. COVID-19 trauma and post-traumatic stress disorder in children and adolescents

The risk of the negative psychosocial effects of the pandemic on the psychological well-being of young individuals has been highlighted (27,28). The majority of children and adolescents exposed to traumatic events develop short-term psychological distress (29); however, in some, particularly in those living in families facing a prolonged complex and stressful situation, symptoms do not remit spontaneously and instead become clinically significant, persistent and impairing (30).

In the context of prior pandemics, a study on families who were quarantined due to SARS or the H1N1 influenza virus and based on parental reports, PTSD was found in 30% of the confined children and in 25% of the parents; this indicated the high traumatic potential of social isolation and living in conditions of constant fear of the disease spreading (31). Longer durations of quarantine have been shown to be associated with

an increased prevalence of PTSD-related symptoms. Indirect or direct exposure to another individual with a diagnosis of SARS has also been shown to be associated with PTSD and depressive symptoms (10). In addition, a study on home-quarantined youth in China during the first month of the COVID-19 outbreak revealed that 12.8% of the participants had traumatic stress levels consistent with PTSD, exhibiting an association with negative coping styles (32). Furthermore, a recent systematic review and meta-analysis estimated the pooled prevalence of PTSD to be 20.7% among Chinese children (33).

Although the COVID-19 pandemic, as mentioned above, is not associated with the development of PTSD in everyone, the pandemic situation increases the risk of multiple traumatic experiences and complex trauma (34). For children living in socially disadvantaged environments characterized by poverty, the lack of access to developmentally appropriate resources, low levels of stimulation and responsive care, or inadequate supervision, the pandemic situation, by aggravated circumstances, may become an adverse childhood experience, generating toxic levels of stress (28).

There is growing neuroscientific evidence to document that early adverse childhood experiences, including prenatal stress and stress throughout childhood, have marked and long-term effects on the development of neurobiological systems (i.e., fronto-limbic circuitry), thereby ‘programming’ subsequent increased stress reactivity and weaker emotion regulation (35). This altered neurobiological response to stress may confer vulnerability to the development of chronic trauma and stress-related disorders, such as PTSD, anxiety, mood and attachment disorders, memory and learning problems, as well as other psychopathological conditions (36).

The COVID-19 pandemic has been described as a ‘perfect storm’ with exposure to known risks and the lack of support affecting the mental health of young individuals

and their families (37). First, prolonged lockdown and severe financial difficulties necessitate changes in family dynamics, which may trigger the use of dysfunctional caregiver coping strategies (e.g., alcohol or substance abuse), family discord, negative parent-child interactions, intrafamilial violence and child abuse (38-40). For young children, unsafe living conditions, in parallel with delays in scheduled healthcare visits and developmental checks, the suspension or interruption of interventions for developmental delays (e.g., language), lost access to child care and early education programs, the disruption of support offered by social services and the loss of supportive social networks, may adversely affect brain development, leading to long-term negative health outcomes (41). Second, for school-aged children and adolescents affected by adverse experiences in early life, i.e., neglect and child abuse or exposure to violence, automatic physiological responses are likely to be reactivated and may further increase the risk of developing PTSD and stress-related disorders. Third, exposure to increased levels of depression, anxiety and psychological distress in adults/caregivers (42), which are potential factors of adversity for cohabiting children and adolescents, may lead to secondary trauma and persistent or delayed-onset distress symptoms. Fourth, given that adolescence is a particularly stressful period due to the occurrence of related developmental changes, such as a marked increase in social sensitivity and interpersonal stress coupled with low tolerance to frustration, a heightened emotional reactivity and a low capacity to effectively engage in cognitive and emotion regulation (43,44), the COVID-19 pandemic, and in particular the prolonged lockdown, may increase the levels of stress in adolescents. Social isolation, the lack of face-to-face contact with peers and teachers due to school closures, a change in daily behaviors (decreased physical activity, increased screen time, irregular sleep patterns and less appropriate diets) and concern for the economic future of their family and country, are among some of the identified pandemic-related stressors that generate psychological repercussions in adolescents (45). A recent study examining the impact of the pandemic, and its related restrictions, on the emotional health of Canadian adolescents found that concerns related to COVID-19, difficulties with online learning and increased family conflict were associated with higher levels of depression and anxiety, whereas feeling socially connected during the COVID-19 lockdown protected the adolescents against poor mental health (46). Given that different types of trauma exposure (e.g., interpersonal or non-interpersonal) probably have differential effects on adolescent cognition and traumatic- and stress-related symptoms, as well as PTSD onset (47-50), and that adolescents rely on peer connections and relationships for their emotional support and social development (51), it is argued that social isolation and social distancing may be an important adversity factor for developing brain systems engaged in social and emotional processes (44). Although it may take years and numerous research studies to fully understand the sequelae of the COVID-19 pandemic during different developmental stages, available data have consistently demonstrated an association of several COVID-19-related stressors with mental health outcomes. Future studies are required to explore these stressors in conjunction with

protective factors and prospective changes in mental health to identify which of these may influence both the typical trajectory of COVID-19-related traumatic experience and the development of psychopathology in the long-term, as well as to determine the underlying mechanisms.

4. Post-traumatic stress disorder and COVID-19 survivors

Scientific evidence from previous epidemics indicates that a severe physical illness can lead to the development of various psychiatric conditions, including, among others, PTSD symptoms following recovery. According to a previous meta-analysis, 17-44% of critical illness survivors, particularly those who required hospitalization and/or admission to an ICU, reported clinically significant PTSD symptoms (52). Due to the fact that the severity of the medical condition seems to be a predicting factor for the development of PTSD symptomatology, the early identification of vulnerable and high-risk patients seems a prerequisite for timely effective interventions (53).

A previous literature review on past coronavirus outbreaks, suggested a high likelihood of COVID-19 survivors developing psychiatric symptoms and disorders, most notably PTSD symptoms (54). Even among individuals who do not meet the full diagnostic criteria for PTSD, post-traumatic stress symptoms (PTSS) have also been shown to be associated with functional impairment (55). As also previously indicated, 42% of individuals who survived MERS presented scores which were above the clinical cut-off for PTSD at 1 year following the outbreak, and almost 26% of individuals who survived SARS met the full diagnostic criteria for PTSD at 30 months following the outbreak (56,57).

In addition, hospitalization is a potentially traumatic experience, particularly in severe cases (58). In spite of this, the vast amount of available research on COVID-19 and mental health is focused on health professionals and the general population. Studies involving hospitalized patients have mainly focused on treatments for the disease (59) and limited information has been reported regarding potential mental health outcomes. Hospitalization, in general, and more specifically, the admission to an ICU may impose a significant burden on the mental health of patients and may lead to the development of diverse conditions, including PTSD and other trauma- and stress-related disorders. Indeed, the highest PTSD rates have been found among patients who had experienced a life-threatening situation in an ICU (14-59%), while the lowest rates were childbirth-related (1.7-5.6%) (60). Hospitalization likely increases the perception of how critical an event is for the lives of individuals, which is usually associated with increased post-traumatic stress (61). In addition, exposure to the severity and life-threatening aspects of the infection may also lead to higher levels of stress and associated reactions (62). This is reasonable, as the development of more severe symptoms may result in an enhanced experience of threat, particularly for symptoms such as dyspnea. Indeed, symptom load was associated with higher levels of post-traumatic stress reactions (6). Patients in the ICU have been found to experience traumatic stress related to both the severity of symptoms and the invasiveness of the medical procedures, which may lead to the development of PTSD symptomatology. In particular, respiratory symptoms can

cause significant distress and fear of respiratory failure (63). Other factors potentially related to PTSD symptomatology include a fear of death, pain from medical interventions, such as endotracheal intubation, a limited ability to communicate and feelings of a loss of control (64). A study among hospitalized patients with COVID-19 indicated that almost 20% of the participants developed significant PTSS within 1 month following hospitalization, which was significantly associated with the length of the hospitalization period and the resulting feelings of social disconnection and mental exhaustion (65). Another study reported a 13.2% prevalence of PTSD among hospitalized patients who were affected by reports of negative news, had a greater exposure to traumatic experiences and lower levels of perceived social support (59). These rates are lower than the prevalence reported by studies on patients with similar infectious diseases, although higher than those in other groups, such as medical residents and medical staff, during the COVID-19 pandemic (66). These findings suggest that hospitalized patients with COVID-19 infection may present with the most adverse mental health issues during this pandemic.

In addition, it has been suggested that a sub-threshold diagnosis of PTSD can be considered a risk factor for more severe mental health outcomes, and more specifically, with an increased risk of depression, suicidal ideation, alcohol consumption and other comorbidities (67). Notably, male gender seems to be a significant protective factor against PTSD. On the other hand, the strongest predictor for the development of PTSD among hospitalized patients with COVID-19 infection appears to be a pre-existing mental health condition (mainly anxiety and depressive disorders), followed by obesity, which similar to chronic pulmonary disease, lead to an increased risk of developing severe disease (58). PTSD, depression and anxiety disorders are often comorbid, linked to high levels of general distress in the acute stage of trauma and are described as a 'symptom network' (59,68).

To summarize, the severity of the medical condition has the potential to determine the future risk of patients to develop PTSD. Research into COVID-19-related PTSD symptomatology and its determinants is of paramount importance in identifying possible modifiable risk factors and vulnerable patients, as well as in evidence-informed decision-making interventions (53). Moreover, effective professional mental health services should be designed to support the psychological wellbeing of inpatients with COVID-19, and particularly those who required hospitalization and/or ICU care.

5. Conclusion

The present review demonstrates that COVID-19 has a substantial impact on mental health and poses a significant risk for the development of trauma-related disorders, including PTSD among individuals who are most vulnerable, such as children, adolescents and COVID-19 survivors (who required hospitalization and/or ICU admission). Therefore, the prompt identification of at-risk populations, early intervention and the effective management of PTSD is of utmost importance. A multi-disciplinary approach should be adopted aiming at enhancing the resilience and coping mechanisms of different sub-groups through early identification, prevention and the

implementation of intervention strategies. Lessons learnt from past pandemics together with the ongoing research on COVID-19 and its mental health consequences highlight the need for evidence-based targeted and proactive mental health interventions aiming at minimizing the potential risks and vulnerabilities.

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IG, SG, EK, MA, IT, SK wrote the original draft, edited and critically revised the manuscript. ER, KT, EA, NS, VZ and DAS critically revised and edited the manuscript. IG and ER confirm the authenticity of all the raw data. All authors substantially contributed to the conception, writing and revision of the work and approved the final content of the manuscript.

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Patient consent for publication

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Competing interests

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