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Neuropsychiatric Manifestations of COVID-19



A Review

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KEYWORDS

• COVID-19 • SARS-CoV-2 • Neuropsychiatry • Psychiatry • Review

KEY POINTS

- COVID-19 is associated with increased manifestation of neuropsychiatric symptoms.
- The presence of neuropsychiatric symptoms may worsen prognosis in COVID-19 infection.
- Screening for neuropsychiatric symptoms in patients with COVID-19 will help with early identification and management of these symptoms and may improve patient outcome.

INTRODUCTION

A pandemic, as defined by the World Health Organization [1], is an epidemic occurring worldwide, or over a very wide area, crossing international boundaries and usually affecting a large number of people. Presently, the COVID-19 pandemic is raging through the USA, and as time is progressing, the larger undercurrent of neuropsychiatric ailments and disorders is making its presence felt. At the time of writing this paper, in the last week of November 2020, 1 year after the detection of the first case of COVID-19 in Wuhan, China, there have been over 57.8 million cases and 1.3 million deaths worldwide [2]. Most patients with COVID-19 present initially with fever (83%–99%), cough (59%–82%), fatigue (44%–70%), anorexia (40%–84%), and shortness of breath (31%–40%) [3]. However, the signs and symptoms present at the illness onset may vary

widely and involve various organ systems. Recent literature is beginning to shed light on the impact of COVID-19 on the nervous system and its neuropsychiatric sequelae.

Studies describing the association between COVID-19 and neuropsychiatric symptoms are limited. Large-scale cohort studies are currently not available in the extant literature. A recent study assessing the potential relationship between COVID-19 and psychiatric disorders found a reciprocal relationship between the two [4]. This study included 62,354 patients diagnosed with COVID-19 with the primary outcomes being the incidence and hazard ratios for psychiatric disorders, dementia, and insomnia during the first 14 to 90 days after a diagnosis of COVID-19 was established. The authors observed that the patients recovering from COVID-19 had a significantly higher rate of psychiatric disorders.

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There was a 5.8% probability of being newly diagnosed with a psychiatric illness within 90 days post COVID-19 diagnosis. The most frequently acquired psychiatric diagnosis was anxiety disorder, with a probability of outcome within 90 days of 4.7%. Among anxiety disorders, adjustment disorder, generalized anxiety disorder (GAD), posttraumatic stress disorder (PTSD), and panic disorder were the most frequent. The probability of a new diagnosis of mood disorder within 14 to 90 days after COVID-19 diagnosis was 2%. Interestingly, previous psychiatric illness was found to be independently associated with an increased risk of being diagnosed with COVID-19. A diagnosis of a psychiatric disorder 1 year prior to the onset of the COVID-19 pandemic was associated with a 65% increased risk of COVID-19 compared with a cohort matched for established physical risk factors for COVID-19, but without a psychiatric diagnosis. This finding held ground in sensitivity analyses.

In this article, we will review and discuss the existing evidence regarding various neuropsychiatric manifestations of COVID-19, including delirium, cognitive impairment, psychosis, depression, suicide, mania, and anxiety in patients with COVID-19 and COVID-19 survivors. We will also discuss the neurobiological mechanisms that are hypothesized to be involved in developing neuropsychiatric symptoms. Furthermore, we will discuss the potential role of medications used for treatment of COVID-19 in causing/worsening neuropsychiatric symptoms. Lastly, we will review the psychosocial factors contributing to the psychiatric presentations of infected individuals considering how important psychosocial factors are in the occurrence of primary psychiatric disorders.

METHODS

We performed a comprehensive search on PubMed and Google Scholar to find all relevant publications on COVID-19 and various neuropsychiatric disorders for this review which were available until November 30, 2020. We used the following keywords for our search: COVID-19 or SARS-CoV-2 and survivors, neuropsychiatry, psychiatry, psychosis, delusion, hallucination, anxiety, mood, depression, suicide, mania, delirium, and cognition. We focused primarily on the studies that described neuropsychiatric symptoms among COVID-19 survivors, as well as patients with active COVID-19 infection.

COVID-19 AND DELIRIUM

Compared to patients with delirium secondary to other comorbid conditions, delirium in COVID-19 patients

has been reported with higher frequency, higher mortality, worse agitation, and a greater likelihood of presenting with specific features, such as catatonia [5]. The incidence of delirium in COVID-19 patients has been reported to be 30% to 50% in various studies [6–9]. One in five patients who died of COVID-19 suffered from encephalopathy [10]. The mortality rate in COVID-19 patients who experienced delirium has been reported to be as high as 55% in comparison to 30% in nondelirious patients [8]. In a study by Garcez and colleagues [8], delirium was determined using the Chart-based Delirium Identification Instrument (CHART-DEL) and it was found to be an independent predictor of in-hospital death. In a case series from Massachusetts General Hospital, the authors reported that in addition to the typical features of delirium, patients displayed significant agitation, increased tone or rigidity, abulia, alolia, and evidence of significant systemic inflammatory response [5]. In a case series from France, out of 58 COVID-19 patients admitted to ICU, 26 scored positive on the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU) scale. Agitation, corticospinal tract signs, and dysexecutive syndrome were seen in 40, 39, and 14 patients, respectively [7]. Diagnostic accuracy in most of these studies appears to be limited as most used retrospective chart reviews for delirium diagnosis or relied on self-report questionnaires from the patients [9].

Delirium and mental status changes in patients with COVID-19 could be due to involvement of various pathways: primary central nervous system (CNS) invasion, secondary to hypoxemia and oxidative stress, or a combination of both. Regarding primary CNS invasion, there are reported cases of encephalitis in patients with COVID-19 with positive cerebrospinal fluid (CSF) PCR, and one reported specific MRI findings [11–13]. The underlying mechanism in these cases could be similar to the pathophysiology of herpes simplex virus (HSV) encephalitis, where the virus spreads via a synapse-connected route to the medullary cardiorespiratory center from the mechanoreceptors and chemoreceptors in the lungs and lower respiratory airways [14]. It is noteworthy that the presence of the SARS-CoV-2 virus in CSF is not required for the occurrence of delirium or encephalitis [7,15]. The other possible mechanism for direct invasion of CNS is via invasion of the olfactory bulb. This hypothesis is based on the observation that patients with COVID-19 have high rates of anosmia and ageusia. It is reported that more than 85% of patients may report anosmia [16]. Delirium could also occur secondary to a systemic response to acute infection, similar to other acute

infectious and metabolic diseases. Hypoxemia, oxidative stress, hypoperfusion, uremia, and acute respiratory distress syndrome (ARDS) that occur in hospitalized patients with COVID-19 are known causes of delirium. Acute full-blown inflammatory response and cytokine storm could be another possible mechanism to explain the high rate of delirium in this population. A combination of both primary and secondary CNS involvement could also occur, similar to encephalopathy due to HIV [5].

Delirium is highly comorbid in patients with COVID-19 and is a significant prognostic factor for poorer outcomes and increased mortality. The risk factors associated with increased rates of delirium in COVID-19 patients and increased risk of death in these patients are not fully understood yet. Some suggest that guidelines for assessment of COVID-19 should include delirium as a presenting feature and its screening should be the standard of care [17].

COVID-19 AND COGNITIVE DEFICITS

In addition to increased risk of altered mental status and delirium, there is some evidence supporting COVID-19's impact on cognitive functioning. This effect has been shown in patients with no prior cognitive impairment, as well as in those with a history of dementia. In their prospective study of 58 patients with COVID-19, Raman and colleagues reported impaired cognitive performance, specifically in the executive and visuospatial domains, relative to controls [18].

Results from previous studies investigating long-term neuropsychological outcomes in patients with medical conditions requiring ventilation indicated declines in several domains of cognitive function. Impairment was shown in memory, verbal fluency, processing speed, and executive functioning. These impairments were noted in 78% of patients, 1 year after discharge, and in around half of the patients, up to 2 years [19–21]. Another study reported memory problems persisting up to 5 years after ARDS, and significantly impacting daily functioning [22]. Moreover, previous studies of sepsis and pneumonia found that mild cognitive impairment and dementia were common in survivors, regardless of infection severity. Given the similarity of acute manifestations of severe COVID-19 and sepsis in general, survivors of severe COVID-19 are anticipated to experience similar cognitive sequelae to sepsis survivors [23].

A small case-control study investigating cognitive impairments in COVID-19 survivors posthospitalization noted cognitive impairment in the domain of

sustained attention in the individuals who had recovered from COVID-19 [24]. However, it was not clear to us whether the study patients had severe illness or not. Additionally, the authors did not use a comprehensive neuropsychological test battery and cognitive deficits in other domains might have been missed.

The mechanisms underlying cognitive impairment in COVID-19 are yet to be investigated. Some speculations include direct damage of COVID-19 to the hippocampus [25], postintensive care syndrome [26], and increased risk of cognitive impairment due to delirium and systemic disease [27]. Raman and colleagues noted tissue changes in thalamus, posterior thalamic radiations, and sagittal stratum on the brain MRIs of patients with COVID-19 who showed impairment in their cognitive functioning [18].

Patients with dementia are more vulnerable to SARS-CoV2 infection and are more likely to have severe disease compared to other individuals [28]. This is mostly due to the shared risk factors of the two diseases, including age, obesity, cardiovascular disease, hypertension, smoking, and diabetes mellitus [29]. COVID-19 can also potentially lead to more severe cognitive impairment in elderly patients, individuals with a history of cognitive impairment, or other comorbid conditions [28].

Overall, the identification of at-risk populations, monitoring of cognitive function for both at-risk and general populations, and study of persistent cognitive impairment and long-term cognitive functioning in patients with COVID-19 appear to be important aspects of addressing neuropsychiatric manifestations of COVID-19.

COVID-19 AND PSYCHOSIS

There are currently few reports of new-onset psychosis in patients with COVID-19 infection. This could likely be explained by two main hypotheses of direct pathophysiological mechanisms and the effect of psychological stressors [30]. A UK study investigating neuropsychiatric symptoms in a COVID-19 database reported new-onset psychosis. In this study, 23 out of 125 patients fulfilled the clinical case definition for psychiatric diagnoses. It was noted that 10 (43%) out of 23 patients with neuropsychiatric disorders had new-onset psychosis [31]. However, such a high prevalence of psychosis was not replicated in other studies, though there have been case reports and case series published on this. One case series reported three COVID-19 patients who presented with new-onset psychotic symptoms but were otherwise asymptomatic [32]. There are also several

case reports of COVID-19 patients who presented initially with psychotic symptoms. These include case reports of patients with SARS-CoV-2-positive test results and no prior psychiatric history who presented with psychosis [33], a COVID-19 patient who presented with command auditory hallucinations [34], and a case report of exacerbated paranoia in a COVID-19 patient with a history of schizophrenia [35].

Neuroinflammatory processes are one of the possible mechanisms of action proposed for inducing psychosis with coronavirus. In a recent rapid review, the authors concluded that exposure to SARS, H1N1, MERS, and coronavirus immune reactivity were associated with recent psychosis [36]. Prior to the current pandemic, some studies suggested infection with certain coronaviruses is associated with recent-onset psychotic symptoms [37,38]. The interaction between psychosis and COVID-19 may be further complicated by the treatment of COVID-19 with high doses of steroids to modulate the inflammatory response since steroids are known to trigger psychotic symptoms [39,40].

In summary, the relationship between COVID-19 and psychosis is not yet established. Most of the available evidence has been gathered through individual case reports and case series. Large-scale systematic studies are needed to elaborate on the relationship between the two.

COVID-19 AND DEPRESSION

COVID-19 has been found to be associated with increased rates of depression in the general population [41], and especially in COVID-19 survivors [42]. Studies of COVID-19 survivors found the prevalence of depression to be 31% to 43% [42–44]. However, in all those studies, depression was assessed using self-rated questionnaires, and not by clinical interview, the gold-standard for diagnosing major depression.

A few studies have attempted to understand the biological mechanisms underlying depressive symptoms in patients with COVID-19. Among these is a study of 402 adult patients who were tested for several inflammatory markers during an ED visit for COVID-19-related systemic or respiratory symptoms, and evaluated various psychiatric disorders after 1-month follow-up in those who were diagnosed with COVID-19 [42]. The inflammatory markers assessed were C-reactive protein (CRP), neutrophil/lymphocyte ratio, monocyte/lymphocyte ratio, and Systemic Immune-inflammation Index (SII). The majority of these patients were hospitalized due to clinical deterioration. No correlation was seen between inflammatory markers and depression, except

for a positive association between baseline SII and depression. The SII highlights the balance between systemic inflammation and immune response. It is a ratio reflecting product from platelets, neutrophils, and lymphocytes, which are all involved in various immune/inflammatory response pathways [45]. In one study, higher SII levels were associated with major depressive disorder (MDD) [46]. Another study [47] compared total and differential WBC counts, neutrophil ratio, lymphocyte ratio, monocyte ratio, eosinophil ratio, basophilic granulocyte ratio, neutrophil-to-lymphocyte ratio (NLR), CRP, and IL-6 between cured COVID-19 patients with and without self-reported depression. They found that WBC count, neutrophil count, NLR, and CRP levels were higher in the self-reported depression group than in the normal group. In a study by Guo and colleagues, no association was seen between depressive symptoms and inflammatory indicators among the entire COVID-19 patient group [48]. However, in this study the patients had mild illness, the inflammatory markers measured were different from the study by Mazza and colleagues [42], and a control group was also used for comparison. This study measured CRP and other inflammatory markers (mainly different white blood cell counts). One interesting finding was that the depressive symptoms were more severe than anxiety symptoms in patients with COVID-19. Among those patients with baseline depressive symptoms (self-reported Patient Health Questionnaire-9 (PHQ-9) score greater than 4), CRP levels positively correlated with PHQ-9 scores. The change of CRP level from baseline negatively correlated with the PHQ-9 score, suggesting that the improved CRP level may have resulted in less depressive symptoms.

It can be safely concluded that more studies are required to elucidate the biological mechanism of the occurrence of depression in COVID-19 patients. There is a possibility that systemic inflammation may be mediating depressive symptoms. This has been noted in previous studies linking inflammation and depression. However, there is no consensus till date regarding which biomarker predicts the occurrence of depression and its severity.

COVID-19 AND SUICIDE

Both clinicians and researchers have anticipated that COVID-19 may lead to an increase in suicidal ideation and suicide attempts. This concern stems from the studies conducted during previous pandemics and infectious disease-related public health emergencies. A

systematic review indicated increased suicide rates among older adults during the SARS outbreak, in the year following the epidemic, and associations between SARS/Ebola exposure and increased suicide attempts [49].

Various psychosocial complications pertaining to COVID-19 may serve to increase the risk of suicide among the general population and patients. For example, lockdowns and social distancing leading to isolation and feelings of loneliness, rising rates of depression, anxiety, substance use, domestic violence, limited access to health services, worsening of physical illnesses, and the trauma of losing family and friends are likely significant factors. Misconceptions, fear, stigma related to COVID-19, as well as financial hardship due to loss of employment may also play a role in increasing the risk of suicide [50]. A recent survey from the Centers for Disease Control and Prevention indicated more than a twofold increase in suicidal ideation of responders in June 2020 compared to a similar survey in 2018. In this survey, 10.7% of 5412 adults reported serious consideration of suicide in the previous 30 days, whereas the 2018 survey reports 4.3% of 10.7 million adults with serious suicidal ideation in the previous 12 months [51]. However, it remains to be seen whether COVID-19 has actually led to an increased number of suicides. Studies that have been conducted to date in Australia [52] and the USA [53] have not yet reported an increase in the number of suicides or suicidal behavior during the COVID-19 pandemic. Similarly, a recent systematic review by John and colleagues [54] did not show an increase in suicide rate or suicidal behavior during the COVID-19 pandemic. Two case reports from India and Bangladesh described two patients who died by suicide and mentioned COVID-19-related stigma as the key driver of the suicides [55,56]. Currently there are no studies which have systematically assessed the risk of suicide in COVID-19 survivors. A meta-analysis of the studies investigating various psychiatric disorders in COVID-19 survivors did not find suicide as its complication/manifestation [57].

So far, no study has evaluated any direct biological mechanism behind suicide risk in those with COVID-19 infection. Considering the tremendous impact of COVID-19 on the global population, it may be too early to conclude that COVID-19 does not increase the risk of suicide. More studies are needed to understand the immediate- and long-term risk of self-harm behavior in patients with COVID-19 and those suffering from its psychosocial impact.

COVID-19 AND MANIA

Numerous studies have linked COVID-19 to depression, whereas the data on mania occurring in COVID-19 patients are scarce. Only a few reports [33,58,59] are available in the literature describing mania after COVID-19 infection. Interestingly, in all those cases, mania occurred for the first time in their lives, and they had very few to none of the risk factors associated with mania. Furthermore, the participants in the study were in the age range of 30s–50s, which is not typical for first-episode mania. One common thread that tied all the cases was the appearance of manic symptoms concurrent with ongoing COVID-19 symptoms.

The neurobiological processes underlying manic symptoms in patients with COVID-19 are unknown. Future studies should carefully survey the occurrence of manic symptoms during COVID-19 infection and in the follow-up period to see if there is a true association between the two disorders.

COVID-19 AND ANXIETY

COVID-19 may increase anxiety symptoms and anxiety disorders in both COVID-19 patients and the general population [41,60,61]. It has also been demonstrated that non-COVID-19 subjects with a preexisting anxiety disorder were more negatively impacted by COVID-19, compared to those with no history of mental illness [62]. A cross-sectional study assessing 402 adults who survived COVID-19 found the prevalence of PTSD, anxiety, and obsessive-compulsive symptoms in 28%, 42%, and 20% of the subjects, respectively [42]. In another study from China, Bo and colleagues reported a significantly high rate of posttraumatic stress symptoms among hospitalized patients. They reported that 96.2% of 714 hospitalized patients with COVID-19 scored higher than the threshold value on the posttraumatic stress disorder checklist-civilian version (PCL-CV) [63].

An increase in anxiety and related disorders may occur through the devastating psychosocial effects of the pandemic and affect various subgroups. These effects are discussed later in this review. However, it is important to note a higher likelihood of the occurrence of PTSD, GAD, panic disorder, and obsessive-compulsive disorder, both as new-onset disorders in vulnerable populations and exacerbation of these disorders among those who already carry these diagnoses. A recent systematic review by Pappa and colleagues showed a higher prevalence of anxiety disorders in healthcare workers [64].

The neurobiological mechanisms underlying an increase in anxiety symptoms in patients with COVID-19 remain to be explored. It has been hypothesized that anxiety in patients with COVID-19 could be due to primary CNS invasion impacting neural circuits related to anxiety, hypoxemia, and oxidative stress, or a combination [42]. In a study by Mazza and colleagues [42], the authors noted that PTSD, anxiety, and obsessive-compulsive symptoms were not associated with oxygen saturation level or inflammatory markers, but were correlated with baseline SII. The SII was also positively associated with anxiety scores at follow-up. However, further studies are needed to investigate infection-triggered changes in the immune system that may also induce anxiety disorders.

PROPOSED NEUROBIOLOGICAL MECHANISMS

The COVID-19 pandemic is novel in its protean manifestation, including the neuropsychiatric ones. Several mechanisms have been proposed for neurotropism of this virus and resultant clinical presentations [65]. Various mechanisms have been proposed for the CNS affliction of SARS-CoV-2, including direct viral invasion, cytokine storm, molecular mimicry, and through systemic illness.

Direct viral injury to the neurons may occur akin to the herpes simplex virus encephalitis. SARS-CoV-2 binds to angiotensin-converting enzyme 2 (ACE2) receptors. These receptors, although highly expressed in epithelial cells of the respiratory and digestive systems, are also expressed in neurons and glial cells in the CNS. These receptors are also highly expressed in endothelial cells, which may serve as a route of entry into the CNS [66].

Cytokine storm may lead to acute or subacute CNS involvement, including encephalopathy. Cytokine storm is a hyperactive immune response characterized by a rapid release of inflammatory mediators [67]. Several studies suggest an association between chronic neuroinflammation and high levels of cytokines and chemokines is involved in the pathogenesis of neurodegenerative diseases such as multiple sclerosis, Parkinson's disease, and Alzheimer's disease [68]. Neuroinflammation has also been found to play a role in the pathogenesis of psychiatric diseases, including mood disorders, schizophrenia spectrum disorders, and substance use disorders, especially alcohol use disorder [69]. Proinflammatory cytokine dysregulation can induce changes in neurotransmitter

metabolism, cause hypothalamic–pituitary–adrenal axis dysregulation, or alter neuroplasticity [70].

Molecular mimicry may lead to bystander effect, such as in the case of Guillain-Barré syndrome [71]. In susceptible individuals, an aberrant immune response may cross-react with both viral antigens and self-antigens [72].

Systemic illness leading to CNS manifestations may also be contributory. For example, peripheral myeloid cells infected by SARS-CoV-2 may subsequently transmigrate to CNS under conditions of increased blood–brain barrier permeability due to inflammation and psychological stress [73].

NEUROPSYCHIATRIC ADVERSE EFFECTS OF MEDICATIONS USED TO TREAT COVID-19

Neuropsychiatric complications can potentially occur as adverse effects of COVID-19 treatment agents. The mechanistic details underlying these complications are largely unknown, and it is often difficult to determine causality. In this section, we will review the evidence regarding the neuropsychiatric side effects of currently used treatment agents for COVID-19.

As of November 2020, the FDA had approved only one drug, remdesivir, for the treatment or prevention of COVID-19, and had authorized the use of a few unapproved drugs under Emergency Use Authorization (EUA). Chloroquine phosphate, hydroxychloroquine sulfate, and COVID-19 convalescent plasma are among the treatment agents that have been granted EUA for treatment of hospitalized patients with COVID-19 [74,75]. Other widely used investigational agents include steroids, IL-6 pathway inhibitors, such as tocilizumab, sarilumab and siltuximab, interferons, favipiravir, ivermectin, and azithromycin [76–78]. A recent study described the role of fluvoxamine, an antidepressant, in preventing serious illness among COVID-19 outpatients [79].

There are no reported major neuropsychiatric events associated with remdesivir to this date [80]. Remdesivir is a nucleotide analogue that blocks the virus replication. In the fact sheet issued by its makers, there is no report of known neuropsychiatric adverse effects in clinical trials [81]. In an open-label cohort of 61 patients diagnosed with COVID-19 and treated with remdesivir, delirium was reported in two patients [82]. However, the causality could not be determined since delirium could be induced by the viral infection itself, or other confounding factors. Other major studies did not report any neuropsychiatric complications induced by

remdesivir. A large clinical trial of 532 subjects using remdesivir versus 516 control subjects reported 12 cases of delirium and altered mental status in the remdesivir group, compared to 12 cases in the control group [83]. The limited available data from other smaller studies do not indicate any major neuropsychiatric side effects associated with remdesivir [84]. However, this drug is still at the investigational stage and the possibility of any neuropsychiatric complications cannot be convincingly excluded.

Neuropsychiatric adverse effects of corticosteroids are common, with a relatively high incidence rate of 13% to 62% [85]. These are complex, unpredictable, and often severe, ranging across most categories of psychopathology, including psychotic, manic, or depressive episodes, or their admixture, cognitive deficits, and minor psychiatric disturbances (irritability, insomnia, anxiety, labile mood). These adverse effects are usually dose dependent. The timing of their appearance is unpredictable, and they could happen immediately after initiation or even after discontinuing treatment. Short-course, high-dose corticosteroid treatment, commonly used in the treatment of COVID-19 infection, may cause delirium and mood changes, with manic symptoms more frequently reported than depressive symptoms [86]. That being said, steroids have also been used to successfully treat COVID-19-associated encephalopathy [87].

There is some evidence concerning the neuropsychiatric side effects of hydroxychloroquine. Both hydroxychloroquine and chloroquine are antimalarial agents with antiinflammatory and immunomodulatory activity. They are known to have neuropsychiatric side effects, most notably, psychosis. Hospitalized patients with COVID-19 are more prone to their side effects, compared to patients with malaria. This increased vulnerability is likely associated with advanced age and possible medical comorbidities of hospitalized patients, such as hepatic and renal insufficiency, which alter the metabolism and clearance of these drugs. Hydroxychloroquine is more widely used, and at present more research is published on the treatment of COVID-19 with hydroxychloroquine, compared to chloroquine, mostly due to its favorable side effect profile [88]. Garcia and colleagues reviewed all psychiatric adverse effects with hydroxychloroquine in 1754 COVID-19 patients registered in Vigibase, the WHO's global database of individual case safety reports, among which they found 56 counts of psychiatric adverse effects. Half of these adverse effects were serious, including four completed suicides, three cases of intentional self-injury, and 12 cases of psychotic disorder

with hallucinations. They also found that the use of hydroxychloroquine was associated with an increased risk of psychiatric disorders compared with remdesivir, tocilizumab, or lopinavir/ritonavir [89]. Moreover, chloroquine and hydroxychloroquine are mild inhibitors of CYP2D6, and have potential interactions with numerous psychotropic medications.

Tocilizumab's neuropsychiatric effects have not been widely studied in the context of COVID-19 treatment. It is a recombinant humanized monoclonal antibody that is used for treating rheumatoid arthritis. It blocks the IL-6 pathway, which could contribute to reducing the inflammatory cascade secondary to cytokine storm seen in many patients with COVID-19 infection. Currently, there is no evidence of induced or increased psychiatric symptoms in patients treated with tocilizumab [90,91]. On the contrary, it has been shown that tocilizumab might have a positive effect on cognition, when used as an adjunctive agent for the treatment of schizophrenia [92].

PSYCHOSOCIAL FACTORS ASSOCIATED WITH COVID-19 AS RISK FACTORS FOR NEUROPSYCHIATRIC DISORDERS

The psychosocial complications associated with COVID-19 are wide ranging, from emotional factors such as loss of loved ones to increased financial burden, while the usual coping and support systems are severely compromised [93]. It is still early for any large-scale study to show how various countries tackling the pandemic are coming up with different and often shifting guidelines [94]. Box 1 lists various psychosocial factors associated with COVID-19 which may increase the risk of psychiatric disorders.

DISCUSSION

The evidence for the increased occurrence of various neuropsychiatric disorders due to COVID-19 infection is still limited but is accumulating with time. Keeping that in mind and based on our knowledge gathered from the studies carried out in the context of previous pandemics and infectious outbreaks, we must anticipate and screen for various neuropsychiatric symptoms among those who carry a diagnosis of COVID-19. Moreover, it is worthwhile remembering that individuals with preexisting neuropsychiatric disorders are more vulnerable to this infection and are likely to experience a more severe course of the disease.

In 1918, during the Spanish flu pandemic, Karl Menninger presented 80 patients with "mental disturbances"

BOX 1

Psychosocial Factors Associated with COVID-19

PTSD/trauma from morbid hospitalization/ICU stay/medical procedures
 Experiencing a near-death situation due to COVID-19
 Experiencing/witnessing death/morbidity in other family members/friends/colleagues who also suffered from COVID-19
 Societal/perceived stigma/isolation (due to quarantine or some other reasons) experienced by patients with COVID-19
 Loss of employment due to contracting COVID-19
 Grave injuries while self-treating COVID-19, leading to morbidity
 Discontinuing (intentional or due to nonavailability of doctors) previous psychiatric/medical treatments leading to recurrence/
 relapse of preexistent psychiatric disorders
 Stress of COVID-19 leading to exacerbation/relapse of preexisting psychiatric disorder

that he associated with influenza. Of those, 16 had delirium, 25 had dementia praecox, 23 had other types of psychosis, and the remaining 16 were unclassified. In his follow-up study, carried out over a period of 5 years, most patients with dementia praecox improved [95]. Similarly, the HIV pandemic is well known to have a significant effect on the brain [96] and is associated with a host of neurologic and psychiatric disorders. From time to time, several virological illnesses with a relatively small area of spread have been shown to cause neuropsychiatric symptoms. Most of these viruses, if not all, are encephalopathic and neurotropic. Examples include West Nile virus, enterovirus 71, Chikungunya, and Nipah [97–99]. Though lethal in their presentation, their effect is offset by limited geographic presence and variable modes of transmission.

Before the COVID-19 pandemic, coronaviruses caused two noteworthy outbreaks: severe acute respiratory syndrome (SARS) in 2002, and Middle East respiratory syndrome (MERS) in 2012. A systematic review and meta-analysis reported the neuropsychiatric presentations of individuals with suspected or laboratory-confirmed coronavirus infection (SARS coronavirus, MERS coronavirus, or SARS coronavirus) [57]. One study reported psychosis in 13 (0.7%) of the 1744 patients with SARS in the acute stage of the disease [100]. Therefore, it is not surprising that our review also indicates possible increased risk of delirium, cognitive impairment, psychosis, anxiety, and mood symptoms in patients with COVID-19.

Some of the strengths of our paper are its timeliness and our focus on elucidation of biological mechanisms underlying neuropsychiatric symptoms due to COVID-19, compared to most other review papers which conflated psychiatric disorders among those at risk of COVID-19 and those who actually got infected with COVID-19. However, this paper should by no means

be considered comprehensive in this area. There are several noteworthy limitations to our study. We omitted all non-English language papers, and our search strategy was limited to the two most widely used search engines.

During this acute phase of the pandemic, mental health professionals are facing unique challenges including caring for patients with serious mental illness and COVID-19 infection [101–103], preventing infection spread in acute psychiatric units, and providing emergency mental health services. In the outpatient world, the practice of psychiatry has transformed over weeks, if not months [104]. Telepsychiatry, which used to account for a small portion of psychiatric services [105], has now become a new norm. A similar transition to telemedicine is also underway for consultation-liaison services [106], and even for emergency psychiatry and inpatient psychiatry units.

The wave of deaths precipitated by COVID-19, its traumatic aftermath, coupled with numerous psychological complications has the potential to change the praxis of psychiatry. In order to serve the needs of our patients and of society, psychiatrists and researchers will need to remain nimble, forward-thinking, and ready to adapt to new situations. Like other medical disciplines, psychiatry will continue to contribute to the constant endeavor of betterment of mankind.

To conclude, there remains a huge knowledge gap in the field of neuropsychiatric disorder and COVID-19, and further studies are required to clearly understand the epidemiology of various psychiatric disorders associated with COVID-19. Additionally, the studies on the etiopathogenesis of those disorders may shed light on their treatments and also help take psychiatric research forward in the process. We remain hopeful of the ability of our profession to help protect humanity from the dangerous impact of COVID-19.

DISCLOSURE

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