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COVID-19 related Psychotic Disorder: Symptomatology in Infected and Uninfected Patients

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ABSTRACT

Introduction: Psychotic disorder has rarely been reported in patients with COVID-19 infection and patients affected by the pandemic but who do not have COVID-19 infection. It is unclear if the disorder occurs due to the stress of the pandemic or due to a cerebral infection of the virus.

Methods: on PubMed, we searched for all reports of patients who developed a new psychosis during the COVID-19 pandemic to review their symptomatology.

Results: Psychotic symptoms were similar in onset, description, duration, and severity in patients who had been infected and those who were affected by the pandemic but did not have the infection. In both groups, most patients were young, without previous psychiatric history, had experienced severe external stress due to the pandemic, had an abrupt onset of symptoms, had intense hallucinations and delusions, and needed psychiatric hospitalization. The disorder commonly lasted about a week, after which antipsychotic medications could be stopped.

Conclusion: External psychological stress and not cerebral COVID-19 infection is the likely cause of psychotic disorder in both infected and uninfected patients.

Keywords: COVID-19, Coronavirus, Psychosis, Psychotic Disorder, Hallucinations, Delusions

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INTRODUCTION

Globally, in September 2021, about 218 million people have had the COVID-19 infection, and about 4.5 million have died due to the infection [1]. Since early 2020 when the pandemic spread, its fear was pervasive and constant [2]. Loss of income, being confined to the house, decreased access to healthcare, social distancing, and masking all led to mass hysteria and hopelessness throughout the world [3]. Anxiety and depression rates increased in the non-psychiatric population [4, 5], and patients with mental illness also experienced exacerbation [6]. Moreover, healthcare providers were not only worried about catching the infection themselves but were also disturbed by the guilt that they could pass it on to their loved ones

at home [7]. Infected patients and their families worried about death and dreaded and felt depressed at the prospect of separation if hospitalization would be needed [8]. The cough, dyspnea, hypoxia, confusion, and the sight of healthcare providers in the hospital in hazmat suits and masks added to the fear and confusion [9], and delirium was found to be common in COVID-19 patients who were admitted in the ICU [10].

Psychotic disorder related to COVID-19 has been reported at a case report and case series level. Since case reports are sporadic, it is unclear how common the disorder is. Previous reviews were commonly on neurological manifestations [3,11-14], a review on the mental health of COVID-19 patients did not specifically address psychosis [5], and some cases of psychosis were almost exclusively in patients who had been infected with other coronaviruses [15,16]. In one review of psychotic disorder in patients infected by a coronavirus, all 24 patients had either SARS-CoV or MERS [15]. In another study [16], only 1 of 14 patients with coronavirus infection had SARS CoV2, the virus which causes COVID-19. Since delirium can be a confounder in the diagnosis of psychotic disorder, some case series used strict criteria to exclude patients with delirium [17,18]. Still, delirium and psychosis were challenging to separate in one series [19], and another series included nine patients who had delirium and one who had psychosis in a single category of “encephalopathy” [20].

Whether most neuropsychiatric symptoms are due to an infection of the brain has been debated [3,21]. It has been speculated that infection of the medullary centers for respiration could be an additional reason for respiratory failure in patients with COVID-19 pneumonia [22]. However, the evidence suggests that anxiety, hypoxia, microemboli, and cytokine storm are the more likely explanations [17]. The psychotic disorder is reported in SARS-Cov2 infected patients and patients who have not been infected but have been socially affected by the pandemic. A comparison of psychotic symptoms in infected and uninfected patients can help determine if psychotic disorder in SARS-CoV2 infected patients could be due to the infection. Some case series [23] and review articles [24] have included infected and uninfected patients. Still, they have not compared these two groups, and it is unclear if their symptomatology is similar and if the severity, duration, and response to treatment are identical.

In this review, our aim was to include all published case reports of patients who had a diagnosis of new psychosis without concurrent delirium and in whom patients either had COVID-19 infection themselves or they had a very close relationship with infection in family members, workplace, in the community, or who were in other ways severely affected by the pandemic.

METHODS

Our primary objective was to find case reports and case series of patients who had SARS-Cov2 (i.e., COVID-19) infection, and secondarily to find case reports and case series of patients who had psychosis in the context of the COVID-19 pandemic but who did not have COVID-19 infection themselves. We searched the PubMed database with only two terms: [COVID] and [PSYCHOSIS]. In April 2021, this identified 220 publications. We scrutinized all these publications and excluded those with no or little relation to our primary or secondary objectives. We reviewed the remaining journals in their full length and reviewed their relevant references to exhaustively find all case reports of new psychosis related to COVID-19 infection. We categorized patients who had the COVID-19 disease and those who did not in separate groups. We summarized the narratives of patients to find similarities and differences in these two groups. We also focused on finding how long psychotic symptoms lasted and how they were treated.

RESULTS

We could find 13 patients in case reports and 59 patients in case series who had COVID-19 infection and reported a new psychotic disorder, mostly without concurrent delirium. We found 31 patients in case reports or case series who did not have COVID-19 infection but developed a new psychotic disorder during and related to the COVID-19 pandemic. The narrative histories of patients are summarized below.

Case-reports of new psychosis without concurrent delirium in patients who were positive for COVID-19

1. Smith et al.,[25] reported a 36-year old female who had COVID-19 infection, and who believed that her partner may kidnap her children and steal her COVID-19 stimulus money. She had ruminative and persecutory thought patterns centering about being ‘tracked by cell phones’. The psychotic disorder lasted 2 weeks. She was treated with risperidone.

2. Chacko M et al.,[26] reported a 52-year old male who thought he was the cause of the epidemic, who on one morning said “Today I should die!,” and tried to cut his neck with a knife. The psychosis lasted under 4 weeks. He had been treated with fluoxetine 20 mg once daily, olanzapine 5 mg twice a day, lorazepam 1 mg twice a day, and he required six ECT treatments. COVID-PCR testing was negative, but IgG was positive after discharge.
3. Lanier CG et al.,[27] reported a 58-year old male who threatened nursing staff, was throwing objects, hallucinating, needed to be restrained, and was diagnosed as having psychotic disorder (unspecified). He was treated with haloperidol 2.5 mg at bedtime and lorazepam 1 mg every 8 hours as needed for agitation. He was well at day 8 and was discharged to home.
4. Lu S et al.,[28] reported a 51-year old male who on day 17 after COVID-19 infection said he was the emperor who could end the current epidemic situation, his great achievements would be recorded in the history, he began to wake up early, speak loudly and was diagnosed to have mania. CSF was positive for COVID-19 specific IgG. Psychiatric symptoms lasted 9 days. He was treated with haloperidol and olanzapine.
5. Lim ST et al.,[29] reported a 55-year old female who on day 15 of COVID-19 symptoms was admitted with visual hallucinations when her cat looked like a lion to her, she saw monkeys in the paramedic's bag, she was seen to be washing her phone in the sink, and was using soapy water to brush her teeth. She swore and spit at nurses and called them devils who will kill her. She was treated with IV Lorazepam, haloperidol 0.5 mg twice a day and discharged on Risperidone. She continued to have paranoid delusions till day 34 and recovered fully by day 52.
6. Losse S et al.,[30] reported a patient who developed psychotic symptoms in the context of acute COVID-19 delirium. It is unclear if the symptoms occurred after the resolution of delirium since no other details or a full-length publication is available.
7. Haddad PM et al.,[31] reported a 30-year-old male who was COVID-19 positive and had progressively more auditory hallucinations on day 10 of quarantine. He believed that ambulance staff and the police wanted to kill him, that helicopters were searching for him, and that he may die due to COVID-19, although he had only mild physical symptoms. His psychosis lasted 7 days. He was treated with lorazepam as needed, risperidone 1 mg two times a day and mirtazapine that was increased to 30mg a day.
8. Mawhinney et al.,[32] reported a 41-year old male who on day 10 of COVID-19 symptoms woke up restless, his ‘brain was racing’, he told his wife that he felt like he was ‘going to die’, and revealed homosexual encounters and other sexual behaviors which his wife said were uncharacteristic. His thoughts were grandiose, persecutory, and religious, and in the hospital, he tried to anoint fellow patients with water. He started writing all experiences, which was “liberating” to him. COVID-19 PCR was positive. The psychotic disorder lasted 12 days. He was discharged on olanzapine 10 mg a day and clonazepam 1 mg twice daily
9. Gillett G et al.,[33] reported a 37 year old male mental health nurse who had COVID-19 infection, who worried that he might infect his family, was preoccupied with biblical passages, saw and heard the devil, was incontinent of urine, and eventually cut his neck and had multiple fractures after he had jumped from an upstairs window .He had features of both delirium and an acute psychotic disorder. Except for flashbacks of his illness, he recovered in about a week. He was treated with olanzapine and as needed diazepam.
10. Majadas S et al.,[34] reported a 63 year old male who was readmitted for psychosis a week after he was discharged on risperidone following a 6-day admission for COVID-19 pneumonia and delirium. At re-admission, the patient had no delirium but he had stopped eating as he believed he did not have an anus, he had auditory hallucinations, and he believed most of his relatives had died. This psychotic episode lasted 2 weeks. He was treated with up-titration of risperidone.
11. Lorenzo-Villaba et al.,[35] reported a 33-year old female with positive COVID-19 PCR who was admitted with auditory hallucinations, unusual behavior, changes in her sleeping habits and incoherent speech. Her psychotic disorder lasted 2 weeks. She was treated with olanzapine 10 mg a day.
12. Clouden TA [36] reported a 46-year-old Spanish speaking female who on day 8 after COVID-19 diagnosis had a constant hallucination of a Caucasian man in scrubs who was always with her in her room, in her car, and in the hospital and who was constantly telling her to come with him and said “I am here for you” in English. She did not sleep as she was afraid he might harm her. Risperidone 1.5 mg twice a day, haloperidol 1 mg a day and trazodone 200 mg nightly helped with insomnia but not the constant hallucination, which lasted 15 weeks and resolved only after she was shifted to quetiapine 25 mg and further increased to 50 mg nightly, and paroxetine 20 mg a day. She was diagnosed with delirium and not psychosis as she otherwise had clear sensorium and intact reality testing.

13. Corres-palacio et al.,[37] reported a 43 year old male who, about a week after an 8-day admission for COVID-19 pneumonia after which steroids were continued for 4 days, had to be brought back to the hospital due to verbal and physical aggression and who resisted arrest with two swords he had in his house. He had persecutory delusions with medical staff and police, visual and auditory hallucinations, did not sleep for days, and had a megalomaniac belief of “communicating directly with God”. His psychiatric hospitalization lasted 1 month, and he was discharged on valproic acid 500 mg every 8 hours, paliperidone 15 mg a day, olanzapine 5 mg a day, and Lorazepam 1 mg prn. His diagnosis was substance/medication-induced manic episodes with psychotic features.

Case series of new psychosis without concurrent delirium in COVID-19 patients

1. Parra A et al.,[17], after excluding 6 patients with delirium, reported 10 patients who had a psychotic disorder. The mean age was 54 years, patients developed psychotic symptoms after about 2 weeks of COVID-19 symptoms. All patients had delusions, 40% had auditory and 10% had visual hallucinations, 50% had been in the ICU for pneumonia, 70% had been taking corticosteroids, and 60 % also had confusional/attentional symptoms. All patients recovered in a maximum of 2 weeks, were treated with low antipsychotic doses, and their delusional symptoms had lasted longer than confusional symptoms.

2. Vartharaj A et al.,[38] reported that in a UK-wide surveillance study of hospitalized COVID-19 patients, 23 patients had new-onset psychosis, 5 had a dementia-like syndrome, and 4 had an affective disorder. New-onset psychoses were more frequently seen in younger patients.

3. Iqbal Y et al.,[18] reported on 9 COVID-19 patients who had no delirium but had new mania or psychosis.

4. Fernando SL et al.,[39] reported on 3 COVID-19 patients, of whom 2 had a prior psychiatric history. These were: a 30 year old male who had auditory hallucinations, saw people chasing him, and he consumed excessive amounts of Pedialyte; a 34 year old female, who had sensations of a “fire burning up inside”; and a 33 year old male who had auditory hallucinations and delusions of his ex-wife and believed that “people with knives and guns in a blue van outside” were trying to kill him.

5. Noone R et al.,[40] reported on 2 patients. Patient A, a 49-year old male, was oriented only to the year, heard voices, had grand delusions of being the devil, confabulated stories of violence at home, and had passive suicidal ideation. Patient B, a 34 year old female, would disrobe in front of strangers, felt she was watched, had persecutory ideas about her landlord, was carrying a knife, and was putting hand sanitizer in her food.

6. Subramanyam AA et al.,[41] reported 3 women in India who had asymptomatic COVID-19 infection and developed new brief psychotic episodes after giving birth. 2 patients had delusions concerning the virus, one believed that medical professionals were trying to infect her baby, and another was acutely paranoid that staff believed that she was spreading COVID-19.

7. Paterson R et al.,[20] reported 10 COVID-19 patients who had transient encephalopathies with features of delirium in 9 patients, and psychosis in one patient. This patient, a 55-year-old female, had ritualistic behavior, delusional thinking, and visual and auditory hallucinations, including seeing lions and monkeys in her house. Her psychotic state persisted past the acute confusional state and resolved after 3 weeks of haloperidol and risperidone treatment.

8. Rentero D et al.,[19] reported new-onset psychosis in COVID-19 patients in Madrid but did not mention the number of patients or the kind of symptoms they had.

9. Jaworowski et al.,[42] reported on 3 male patients who had COVID-19 infection. All had a brief psychotic disorder that resolved over 2 days with parenteral neuroleptic medication. All three had grandiose and religious delusions. One had been fined for transgressing social distancing restrictions, and had been using cannabis daily.

Case reports or case series of new psychosis related to the COVID-19 pandemic in patients who themselves did not have COVID-19 infection

1. Oca Rivas VC et al.,[43] reported a patient who was a healthcare professional who did not have COVID-19 infection but had reactive psychosis, including a conviction that his death due to COVID-19 was near. He dramatically searched online for information about COVID-19, and had a psychiatric hospitalization for depersonalization, thought blocking, and delusions. After one month of olanzapine intake, he was better but had not yet returned to work.

2. Hurcaya-Victoria J et al.,[44] reported a 38-year-old female in Peru who became anxious after visiting a dentist who had returned from France and did not wear a mask. She had no COVID-19 infection but was in a 15-day quarantine for malaise when she complied with increasing voices commanding her to be re-tested. “An evil demonic force possessed her

soul,” and she unsuccessfully tried to kill her family. Symptoms lasted 11 days. She was treated with quetapine 500 mg a day and clonazepam 1 mg a day.

3. Zulkifli NA et al.,[45] reported a 31-year old male in Malaysia who became very concerned about COVID-19, caused a public “nuisance”, held a knife and said that the world was going to end. Symptoms resolved after antipsychotic medications were given during three days of hospitalization.

4. D’Agostino A et al. [46] reported six patients in Italy who did not have COVID-19 infection but had delusions of being infected. All had religious/spiritual delusions and hallucinations. None had a previous psychiatric history. Detailed symptomatology was reported for all patients, and all met the criteria for Brief Psychotic Disorder. Hospitalization ranged from 6 to 25 days, but in 5 of 6 patients, psychotic symptoms had resolved within a week of antipsychotic treatment...

5. Chandra PS et al. [47] reported two patients. Case 1 was a 34-year-old city-dwelling female housekeeper in India who did not have a COVID-19 infection. Still, due to the lockdown, she could not travel to her village to fulfill a religious ritual on the day of a Hindu festival. Subsequently, she heard voices that the curse of their family deity would kill her and her family. Symptoms improved after a week of risperidone and clonazepam. Case 2 was a 24-year-old post-partum patient who became agitated with psychosis when her baby girl was in the ICU, COVID-19 was raging in India, and her family criticized her for giving birth to a girl. She also did not have the COVID-19 infection but was afraid that breastfeeding would infect her child. She has been treated with olanzapine 20 mg daily and lorazepam for catatonia.

6. Finnati F et al. [48] reported 3 cases. Case 1 was a 30-year male patient whose parents were hospitalized with COVID-19, but he did not have the infection. He was admitted due to delusions about his parents and that his home quarantine was a scheme to keep him contained. He had visual hallucinations and destructive rage. Case 2 was a 40-year-old female who, due to the pandemic, forbade anyone from leaving the house, prayed obsessively, imposed religious rituals on her husband, had delusions about being forced to return to Romania, and that thieves were hidden in her house. Case 3 was a 40-year-old male who, during quarantine, was reminded of his brother’s death in a car accident, had guilt regarding this death, had delusions of loss and ruin, fear of technology, and suicidal ideation. In all three patients, psychosis resolved in 3 days of treatment with risperidone 2 to 5 mg a day, diazepam 2 to 6 mg a day, and paroxetine 20 mg a day.

7. Shanbour A et al. [49] reported 3 cases, none of whom had COVID-19 or psychiatric history. Case 1 was a 23-year old male living alone in his dorm on a vacant college campus and had delusions about being God’s messenger regarding COVID-19, that 5G cell phone towers were spreading the virus. Case 2 was a 30-year-old woman who was not sexually active and had regular menstrual periods but had the delusion of being pregnant, and that her pregnancy tests were negative due to COVID-19. Case 3 was a 37-year-old male who had auditory hallucinations, religious preoccupations, and delusions of being God’s son who could spread the word of God and save his family from COVID-19. In all three patients, delusions improved incompletely with a long-acting second-generation antipsychotic medication.

8. Mahapatra et al.,[23] reported on 3 cases. Case 1 was a 48-year-old male hospitalized for COVID-19 and whose mother died simultaneously due to COVID-19. He had grandiose ideas and wanted to instruct the Prime Minister on how to manage the pandemic. He had mania which lasted two weeks. He had been treated with olanzapine 15 mg a day and titrated clonazepam. Cases 2 and 3 were 14 year and 9-year-old girls, respectively, and both did not have COVID-19. The 14-year old was treated with risperidone and lorazepam for a one-week episode of psychosis that developed after she could not keep up with online school lessons during the lockdown. The 9-year old developed fainting spells after her family’s finances plummeted during the lockdown, and she needed a month of psychotherapy for conversion disorder.

9. Lazzari C et al. [50] reported on 6 cases who did not have COVID-19 but had paranoid delusions, and two patients had olfactory and visual hallucinations. One tried to kill his family to save them from the consequences of COVID-19. All patients had mania, violence, disinhibition, severe anxiety, and loss of financial wisdom. All responded well to varying regimens of antipsychotic, antidepressant, antianxiety, and mood-stabilizing medications. All recovered fully after a week of hospitalization.

10. Fischer M et al.,[51] reported a 43-year old male who was admitted with hearing voices of his neighbors blaming him, as a former ambulance man, for not taking care of his parents who could have died due to COVID-19 and for spreading the disease. He was not reported to have COVID-19 himself. He believed that cameras were watching him and that he was

immune to COVID-19 infection by a Chinese message on Whatsapp. He did have a history of chronic schizophrenia, but this had been stable with treatment with depot paliperidone. His acute psychosis resolved before discharge. He had been treated for this with olanzapine 25 mg a day and Lorazepam 2 mg a day.

11. Valdés-Flórido et al.,[52] reported 4 cases. Case A was a 33-year old male whose job was under threat due to the pandemic; he thought his loved ones were controlled by machines and tried to commit suicide. Case B was a 43-year-old female with a history of bipolar disorder who had a psychotic relapse due to home confinement. Case C was a 43-year-old female who had a delusion that she was a COVID-19 carrier and her friend had died due to this. Case D was a 45-year-old male who obsessively followed the global death toll of the pandemic, which he thought was caused by the Illuminati; he could hear his neighbors commenting on his thoughts and attempted suicide and thought he would be tortured. All cases were treated with usual antipsychotic medications and recovered fully in 2 days to 3 weeks.

DISCUSSION

Our findings

Our review found that psychotic disorder related to COVID-19 is reported rarely, and infected versus uninfected patients have a similar frequency, severity, and duration of psychotic symptoms. Most patients in both groups had an abrupt onset of a first-time extreme psychiatric dysfunction. However, they usually recovered in about a week and barring exceptions all patients recovered almost fully in about a month.

We did not do a systematic review because the number of infected or uninfected patients in case reports and case series is minimal. It is impossible to make a statistical comparison of infected and uninfected patients' qualitative experiences and circumstances. However, for these reasons, our inferences can also be only subjective. Also, there might be unpublished case reports or ones that we could not find. Although the severity of symptoms is such that all patients will present for emergent care, their case histories may not get reported due to the constraints of the pandemic. In our review, case reports of psychotic disorder were fewer in patients who did not have COVID-19 infection. This may have occurred because patients without COVID-19 disease may get reported less often. If more cases are reported, then more differences might be found in the narratives of infected and uninfected patients.

Psychotic disorder is reported rarely in COVID-19 related patients

We found case reports or case series of only 103 patients who had a new psychotic disorder in the context of COVID-19 whether or not they had COVID-19 infection. The diagnosis of the psychotic disorder may have been missed in unpublished reports since milder confusion is widespread in COVID-19 patients, and delirium is common in COVID-19 patients in the ICU. Even in the few case reports, we found some patients had delirium or had transitioned from delirium [20,30,33,34,36]. In one series, it was challenging to separate delirium from psychosis [19]. One of the DSM-5 criteria for delirium is a disturbance in cognition [e.g., memory deficit, disorientation, language, visuospatial ability, or perception]. This overlaps with psychotic disorders, which involve hallucinations, delusions, disorganized thinking, or grossly disorganized motor behavior [53]. Diagnostic criteria should be strictly applied since antipsychotics are not recommended for patients in delirium. [54]. If cases with delirium are excluded, then as compared to the 4.4 12-month prevalence rate of psychotic disorder per 1000 people in the population [55], and as compared to the millions of patients who have had COVID-19 infection, COVID-19 patients appear to develop psychotic disorder very rarely. This is consistent with a review that found that 0.9% to 4% of patients develop psychotic symptoms [3]. Mania, psychosis, and delirium were reported in patients who had the Spanish Flu in 1918 [56,57], and focus or psychosis occurred in only 0.7% of SARS and MERS patients [3].

Symptomatology was similar in infected and uninfected patients

In the case reports we reviewed, in both infected and uninfected patients, the narrative, duration of symptoms, response to treatment, and the COVID-19 context in their symptomatology appeared similar to the point of being indistinguishable. Patients who had the infection experienced a new striking and severe but relatively brief and easily treated psychotic disorder within days of acquiring the infection. The temporal relationship with the infection strongly suggests a causative role, either as a direct neurotoxic effect or indirectly through an effect on other body systems or inflammation. However, this assertion becomes questionable since almost the same kind of brief psychotic disorder occurred in patients with no infection. Since patients without the infection also had no prior psychiatric history, their new psychotic disorder must have occurred due to anxiety alone, especially because in all these patients the pandemic had disastrously affected their family or their own life. This is

not surprising since the pandemic has been highly threatening to all people, and even those who are highly balanced psychologically have had to be strong. [4,5,58]. Our findings suggest that psychotic disorder in infected patients, as in uninfected patients, was likely due to extreme mental stress and circumstances related to the COVID-19 pandemic and not due to the infection by the virus per se. Additionally, infected patients may experience post-traumatic stress disorder, which occurs in almost a third of patients who have had critical illness due to any cause [59]. In one series of COVID-19 patients, delirium was followed by psychotic disorder [19].

Multifactorial delirium does occur commonly in COVID-19 patients in the ICU

Delirium is reported much more commonly, and 65% to 70% of COVID-19 patients in the ICU had delirium [13]. Although transient disorientation and perceptual disturbances can occur in both [60,61], unlike psychosis, delirium has underlying factors, increasing in ICU patients with COVID-19 [62]. These include hypoxia, co-morbidities related to advanced age, metabolic abnormalities, polypharmacy including the use of steroids and experimental antimetabolic and antiviral medications [16], presumably the effect of isolation due to the inability for the family to visit and of alienation, because providers of health care can be unrecognizable in their hazmat suits and masks.

Neuropsychiatric symptoms and psychotic disorder in COVID-19 patients in media

COVID-19 is a new challenge. Even though many patients have been infected and have died, the pandemic is only 1.5 years old, and there has not been enough time to know all details about how the virus affects us. Due to this lack of information and the fear of the virus, many opinions have surfaced in public. Some of them are incorrect [63, 64]. It is well known that the respiratory and digestive tracts are affected. But a new loss of taste or smell, confusion, “brain fog,” and inability to stay awake are also characteristic [65]. These symptoms have raised the concern that the virus can also affect the nervous system and that patients can have psychiatric effects [66]. A news item [67] in November 2020 reported that “about 20-25% of patients are getting psychosis diagnosis months after recovery” in patients who have had no previous psychiatric history. In our review, we found a much lower frequency and duration of symptoms. In December 2020, the New York Times reported that a small number of patients developed psychosis but presented examples of very severe psychosis in many patients [68]. However, a subsequent news report in January 2021 emphasized that psychotic disorder is infrequent in COVID-19 patients [69].

Neurological effects are common but evidence is weak for a neurological infection by the virus

The concern that the COVID-19 virus can cause psychotic disorder could be because of the neurological effects of COVID-19, which are much more common and were reported in 36.4% of all and 88% of severe ill COVID-19 patients [70]. Strokes, seizures, encephalitis, Guillain-Barre like nerve damage, and severe forms of meningio-encephalitis have been frequently reported [11,12,71]. Biological evidence for neurotropism of the virus is conflicting. The virus was found in the CSF of some COVID-19 patients [11,72,73], and it was reported in the CSF of SARS and MERS patients [74]. Still, it was not found in any of the seven patients with neurological symptoms in which it was tested [13], in a patient with encephalitis, [72] or in other series and reviews [15,24,75].

On brain autopsies, the virus was found at very low levels, and that too was reported to be likely contamination from blood [76]. ACE-2 receptors, which are required for the virus to attach to host cells, are present on brain cells in very low amounts, although a few are present on oligodendrocytes [75]. In vitro evidence of neuroinvasion by the virus has also been reported in one study [77]. A cardinal early symptom in COVID-19 is the loss of smell. Still, the virus does this through damaging olfactory epithelial cells, which express ACE-2 receptors and not by affecting olfactory neurons, which it cannot invade since they do not express ACE-2 receptors [66]. Injury to the brain due to hypoxia, microthrombi, sepsis, and cytokine storm [75,78] are hypothesized to be more likely factors than a neuronal infection. In the vast majority of patients, there is no evidence of viral CNS access [24]. In summary, although neurological symptoms are prevalent, the laboratory evidence is currently weak for a direct invasion by the virus into the CNS [3,14,20].

Etiology of psychotic disorder in COVID-19 patients

Whether the virus infects the CNS in COVID-19 patients and whether CNS infection is the cause of psychotic symptoms have been the subjects of previous reviews [3,24,66]. Historically, the risk of a diagnosis of psychotic disorder is high after severe infections, especially viral respiratory infections and influenza-like epidemics [3]. However, the evidence is scant for any neuronal invasion by the COVID-19 virus. This is true for COVID-19 patients with either neurological or psychotic symptoms [3, 20,24,66].

Autoantibodies against brain antigens can be an explanation for psychotic symptoms in COVID-19 patients since they meet several criteria for the diagnosis of cycloid psychosis [79], which is similar in presentation to autoimmune NMDA [N-methyl-D-aspartate] receptor antibody encephalitis [NMDARA encephalitis] [79].

In cyclops psychosis, patients have episodic psychosis with complete and rapid recovery between episodes, and in DSM-5 cyclops psychosis, patients have brief or unspecified psychotic disorders [80]. In NMDARA encephalitis, autoantibodies that block the glutamate NMDA type receptor are found in serum and CSF, and the blockade can lead to hallucinations [81] and some symptoms of schizophrenia [82]. NMDA receptor antibody was found in CSF in a patient with COVID-19 infection [83], in the CSF of a patient who was not infected with COVID-19 but was affected by the COVID-19 pandemic, [84], and in the serum or CSF of all 11 patients who were critically ill due to COVID-19 infection but without psychotic symptoms [85]. However, autoantibodies to brain antigens are also found in healthy people, and their prevalence in psychosis and the general population was found to be almost the same [86].

In our review, we found that the symptom profile of COVID-19 patients with psychosis matched the profile [79] of patients who had NMDARA encephalitis in many ways: [a] no previous psychiatric disease, [b] young age usually between 15 to 50 years of age, [c] onset of acute psychotic symptoms within hours to days, [d] symptoms of confusion, hallucinations, delusions, paranoia, and a concern with death. They also had a “post-infectious” onset and a preceding flu-like prodrome [24,87] similar to COVID-19 infected patients or had external or family stress [79] as a trigger as in COVID-19 uninfected but affected patients. However, very few NMDARA patients have only acute psychosis [87], and unlike COVID-19 patients, many NMDARA encephalitis patients have progressive neurological worsening with seizures, catatonia, hypoventilation, and even death [87]. Also, unlike patients with COVID-19 related psychosis, NMDARA encephalitis patients are intolerant of antipsychotic medications and respond better to anti-inflammatory medication. [79,87].

Psychotic disorder in COVID-19 patients may be due to the stress of the pandemic

We found very few case reports of psychotic disorder in COVID-19 patients, and the disease is rare considering how common the infection has been. We found even fewer case reports of patients who had no COVID-19 infection. The disorder was short-lasting in the vast majority of patients in both groups. We also found that subjective symptomatology, severity, duration, and response to treatment are very similar in infected and uninfected patients. This similarity of rare occurrence, short period, and severity suggests that symptoms in infected patients are also due to external stress related to the pandemic and not due to a CNS infection by the virus.

CONCLUSION

Case reports of psychosis are rare in patients with and without COVID-19 infection. In both groups, the severity and abrupt onset of extreme symptoms made psychiatric admission essential. Also, almost always, in both groups, symptoms dissipated quickly within days to weeks, and anti-psychotic medication could be stopped. The etiology remains elusive. Symptoms were unlikely due to a CNS infection by the virus because infected and uninfected patients experienced similar symptoms, and the standard trigger in both groups was the external stress due to the pandemic.

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Authors' contributions

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Conflict of interest

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