

Brief psychotic disorder associated with quarantine and mild COVID-19

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SUMMARY

A 30-year-old man with no significant previous or family psychiatric history became severely anxious about his health after a positive COVID-19 test. Physical symptoms of COVID-19 were mild, with no evidence of hypoxia or pneumonia, throughout his illness. He was admitted to a quarantine facility. He remained highly anxious, and 1 week later, he developed paranoid delusions and auditory hallucinations (his first psychotic episode). He was treated with lorazepam 1 mg four times a day, mirtazapine 30 mg nocte and risperidone 1 mg two times a day. His psychotic symptoms lasted 1 week. He stopped psychiatric medication after 4 weeks and had remained well when reviewed 3 months later. A Diagnostic and Statistical Manual of Mental Disorders fifth edition diagnosis of brief psychotic disorder with marked stressor (brief reactive psychosis) was made. Anxiety about his health and social isolation appeared the main aetiological factors but an inflammatory component cannot be excluded. The case highlights that first episode psychosis can be associated with mild COVID-19.

BACKGROUND

COVID-19 was first reported in Wuhan, China, in December 2019. It is caused by infection with SARS-CoV-2, an enveloped single-strand RNA virus.¹ The disease spread rapidly across the world and in March 2020 was declared a pandemic by the WHO.² There have been increasing reports of people developing short-lived first episodes of psychosis, other than delirium, at the time of, or soon after, a positive test for SARS-CoV-2.³⁻⁵ First episodes of mania have also been reported in association with COVID-19.^{6,7} The association between COVID-19 diagnosis and psychosis may be spurious, but in many cases, the details strongly suggest a causal link. Various aetiological pathways may operate including psychosocial stressors associated with infection precipitating psychosis in vulnerable individuals. Examples of stressors include anxiety about health, fear of death and social isolation. Quarantine is well documented to have adverse psychological effects including causing anxiety and anger.⁸ A report from Italy described three patients who developed a first psychotic illness while quarantined for COVID-19.⁹ Brief psychotic episodes have also occurred in people experiencing psychological distress related to the pandemic but not infected with SARS-CoV-2.¹⁰ In some cases, the psychosis has been accompanied by suicidal behaviour.⁹

Organic factors may cause psychosis in patients with COVID-19, especially if there is pneumonia

and significant systematic complications.⁴ Psychosis may be related to inflammatory changes and metabolic dysregulation associated with COVID-19 and iatrogenic effects of medical treatment. For example, corticosteroids were implicated as a contributory factor to cases of psychosis associated with SARS.¹¹ SARS-CoV-2 is associated with a hypercoagulable state that can lead to macrovascular and microvascular cerebral infarcts, which could also contribute to the onset of psychosis.¹² Finally, SARS-CoV-2 may be neurotropic.¹³ Other coronaviruses, including SARS-CoV and Middle East respiratory syndrome coronavirus (MERS-CoV), are known to be neurotropic.¹³ In support of this possibility, SARS-CoV-2 RNA had been detected in the cerebrospinal fluid of patients with neuropsychiatric complications of COVID-19 including encephalitis¹⁴ and meningitis.¹⁵ However, at present, such cases appear rare.

We report the case of a man, with no significant previous or family psychiatric history, who developed severe anxiety about his health after receiving a positive COVID-19 test. He was admitted to a quarantine facility and soon after developed psychotic symptoms. Throughout, he had only mild physical symptoms of COVID-19. A diagnosis of the Diagnostic and Statistical Manual of Mental Disorders fifth edition (DSM-5) brief psychotic disorder (BPD) with marked stressor (brief reactive psychosis) was made.¹⁶ We discuss the differential diagnosis and his management in the light of the existing literature.

CASE PRESENTATION

In May 2020, near the height of the COVID-19 pandemic in Qatar, a 30-year-old man called an ambulance reporting generalised aches and being unable to sleep due to anxiety about his health. He was taken to a major hospital. His symptoms started 4 days earlier after he received a positive COVID-19 test (RT-PCR) that was arranged after a friend had tested positive for COVID-19. Since then he had been searching the internet and social media for COVID-19 information and repeatedly telephoning friends and relatives to seek reassurance about his health. He had no cough or other physical symptoms. Physical examination in the emergency department was normal other than a mild fever (37.9 °C). All subsequent temperature readings throughout his illness episode were normal. Chest X-ray was clear. Peripheral oxygen saturation was 99%. Blood tests, which included full blood count and metabolic profile, were normal apart from an elevated ferritin (623.0 µg/L). C reactive protein (CRP) was normal (<5.0 mg/L). He was diagnosed



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with mild COVID-19 (ie, positive PCR test, symptomatic but no evidence of viral pneumonia or hypoxia).¹⁷ With his agreement, he was transferred to a government run quarantine facility which was consistent with public health policy at that time. The patient was from South East Asia and had worked as a storekeeper in Qatar for the last 12 years. His family lived abroad in his home country.

On admission to the quarantine facility, he commenced the standard protocol for COVID-19 at that time, namely, azithromycin, ceftriazone, subcutaneous enoxaparin, hydroxychloroquine plus paracetamol prn. Two days later, azithromycin and hydroxychloroquine were stopped due to an increased corrected QT interval (QTc) (533 ms). Over the following days, his QTc normalised. He continued to experience insomnia and anxiety.

Ten days after admission to quarantine, he was transferred to a medical ward in the hospital because of increasing agitation, insomnia and vague reports that he had heard voices for 3 days prior to his transfer. His description raised the possibility that he was experiencing auditory hallucinations. The purpose of the hospital admission was to allow a thorough assessment by the internal medicine and consultation liaison (CL) psychiatry teams. On admission to hospital, physical examination including full neurological examination was normal. An ECG, chest X-ray and blood tests (complete blood count and metabolic profile) were also normal. He was seen by a consultant psychiatrist from the CL team on admission. His grooming and self-care were reasonable. He was restless and agitated, which hindered the assessment. His speech was normal in tone, rate and form. He was preoccupied by worries about his COVID-19 diagnosis and his physical health. He had no thoughts of self-harm. He was fully orientated in time, place and person with no evidence of memory impairment. No psychotic symptoms were detected. A diagnosis of acute stress disorder was made, he was offered reassurance and lorazepam 1 mg four times a day was prescribed.

He was reviewed again by a CL consultant psychiatrist 3 days later. He gave a more detailed history; this appeared to reflect the fact that he was calmer, presumably due to the effect of the lorazepam. He was alert, focused on the interview and gave a clear history. He reported feeling guilty about originally attending hospital by ambulance. He believed that the ambulance staff and the police wanted to kill him for calling the ambulance. These beliefs met the criteria for delusions, that is, they were false, held with absolute conviction, were not amenable to reason and were inconsistent with his education and culture. He reported having had these beliefs for the last 3 days. He was also concerned that helicopters might be searching for him and he gave a vague description of hearing voices for several days. He was worried he may die from COVID-19 despite his mild physical symptoms. He reported low mood, anxiety, lack of interest and insomnia. He reported normally getting 7 to 8 hours sleep per night but that he was now only sleeping for a couple of hours per night. His appetite was poor and he attributed this to a recent loss of his sense of taste and smell. He denied suicidal thoughts. He was fully orientated in time (time, day, date, year), place (building, town, country) and person. He highlighted that he had forgotten his mobile phone at the quarantine facility when he had been transferred. As a result, he said that he felt more isolated as he could no longer contact his family.

He denied any previous medical or psychiatric history other than a brief period of anxiety over nose bleeds 7 years earlier. This had resolved spontaneously and did not lead to a mental health consultation and was not associated with psychotic symptoms. He was a non-smoker and had never used alcohol or illicit drugs. There was no family history of psychiatric illness. A

collateral history from a friend, who had known him for 9 years, and who had recently liaised with his family in his home country, confirmed that there was no previous psychiatric history. The patients' native language was Hindi but he also spoke good English. English is the language used by all medical professionals in Qatar and so the patient was able to communicate freely with the medical and CL teams caring for him. In addition, some members of staff on both teams spoke Hindi enabling assessment in the patient's native language.

INVESTIGATIONS

Given the sudden onset of psychotic symptoms a CT head scan was arranged and was normal. Full blood count and biochemical profile were normal other than a mild leucocytosis ($14.0 \times 10^3/\mu\text{L}$). CRP was also normal ($<5.0 \text{ mg/L}$) but a few days before his psychotic symptoms appeared it had been mildly elevated (12.3 mg/L).

DIFFERENTIAL DIAGNOSIS

A diagnosis of a first psychotic episode was made by the CL team. The next step was to clarify its nature. The abrupt onset of psychotic symptoms (paranoid delusions and auditory hallucinations) following a period of significant anxiety about being diagnosed with COVID-19 strongly suggested a BPD with stressor (ie, brief reactive psychosis), a diagnosis that appears in DSM-5.¹⁶ The DSM-5 diagnostic criteria for BPD are a sudden onset of a psychotic episode, one or more psychotic symptoms (either delusions, hallucinations or disorganised speech), duration of more than 1 day but less than 1 month, eventual full return to premorbid level of functioning, and that the disorder is not better accounted for by alternative diagnosis, for example, substance use, a medical condition, schizophrenia or a mood disorder.¹⁶ When BPD occurs in response to a stressful event, DSM-5 requires that the specifier BPD 'with stressor' (also termed 'brief reactive psychosis') is used. DSM-5 recognises two other subcategories of BPD, namely, BPD without marked stressor and BPD with a postpartum onset. BPD is usually a retrospective diagnosis. Follow-up showed that the patient's psychotic symptoms lasted 7 days, the whole illness episode lasted less than a month and there was a total return to normal functioning. As such the DSM-5 BPD criteria were met.

Differential diagnoses were considered but excluded. These included delirium and a psychotic disorder secondary to another medical condition or medication or substance use. The principal diagnostic criteria for delirium in DSM-5 are (1) impaired attention and awareness, (2) evidence of other cognitive impairment, (3) acute onset with symptoms tending to fluctuate during the day (usually worse at night) and (4) evidence that the syndrome is a direct physiological consequence of another medical disorder, exposure to a toxin, intoxication or withdrawal from a substance.¹⁶ These criteria were not met. In more detail, throughout the illness episode, the patient did not show inattention (eg, he could focus during interviews, give a clear history and he was not distractible) or reduced awareness (he was fully orientated), there was no evidence of additional cognitive impairment (unless auditory hallucinations are considered within this domain), and he not display diurnal symptom variation. These findings were consistent across repeated assessments made by the CL psychiatry team and were supported by observations made by the ward nurses. The CL team routinely assess orientation in all patients with COVID-19 in terms of time (time, day, date, year), place (building, town, country) and person. Formal tests of cognition (other than orientation) were

not conducted but there was nothing during repeated interviews, and on general nursing observations, to suggest deficits in memory, language or visuospatial ability. For example, his self-care was good, he provided clear and consistent information and where facts (eg, home and work address, phone numbers) were corroborated from independent sources, this revealed no contradictions. The patient had no visual illusions or visual hallucinations; both are common features of delirium. A DSM-5 diagnosis of delirium requires evidence of a concurrent physical disorder that could account for the syndrome.¹⁶ This criterion was not met. During his hospital admission, the patient was under the care of physicians on a medical ward and as such he underwent thorough and ongoing medical assessment. This included a full physical examination on admission, five times daily monitoring of physical signs (temperature, pulse, blood pressure, pO₂) throughout the admission (approximately 2 weeks duration), blood tests including full blood count and metabolic profile on several occasions, ECG, chest X-ray and a CT head scan. None of these assessments/investigations revealed any abnormality, other than a mildly elevated CRP and white cell count. In the context of his overall clinical picture, neither was regarded as significant by the medical team. Other than his anosmia and ageusia, he was asymptomatic for COVID-19 during the admission. He was not diagnosed with any physical comorbidity or complication of COVID-19 by the medical team. In summary, a diagnosis of delirium was excluded on multiple grounds.

The lack of cognitive impairment and neurological signs excluded an encephalopathy or encephalitis presenting with psychotic symptoms. The absence of neurological signs and the normal CT head scan ruled out a brain tumour or cerebral infarct contributing to the clinical picture. The patient had never used illicit drugs or alcohol, excluding a drug-induced psychosis. Corticosteroids and certain other medications, including anti-parkinsonian agents, can cause psychotic symptoms, but the patient did not receive any such medications.

Although the patient had depressive symptoms, a depressive psychosis was regarded as unlikely. In particular, subsequent follow-up showed an illness duration with full recovery in less than 4 weeks with psychotic symptoms present for 1 week of this period. Such a short time course would be highly unusual for a depressive psychosis. Schizophrenia was ruled out as in DSM-5, it requires an illness duration of at least 6 months with psychotic symptoms being present for at least 1 month of that period.¹⁶

TREATMENT

The patient was offered reassurance and support from both the medical and psychiatric teams. He displayed poor insight into his paranoid beliefs but was aware that he had been having problems with sleep and mood. The diagnosis of psychosis was discussed with him. Although he remained adamant about the reality of his paranoid beliefs, he agreed to engage with the treatment plan proposed. His telephone was brought to him from the quarantine centre, where he had forgotten it, to help reduce his isolation. He was commenced on risperidone 1 mg two times a day and mirtazapine 15 mg/day which was increased to mirtazapine 30mg/day a few days later. He continued lorazepam.

Risperidone was commenced to treat his psychotic symptoms and mirtazapine to treat depressive symptoms. The decision to prescribe mirtazapine was partly pragmatic. When it was commenced, the patient was experiencing low mood, lack of interest, guilt, impaired appetite, insomnia and psychomotor agitation (ie, depressive symptoms). These symptoms had appeared gradually following his COVID-19 diagnosis.

Insomnia and anxiety were the first symptoms to appear and had been present for just over 2 weeks. Strictly, the minimum duration criteria for major depressive disorder (MDD) were not met i.e. not all his depressive symptoms had been present most of the time for at least 2 weeks.¹⁶ One option was to continue to monitor his depressive symptoms ('watchful waiting') and commence an antidepressant if and when MDD criteria were definitely met. The alternative option, and the one adopted by the treating consultant, was to commence mirtazapine at that point in an attempt to treat what appeared to be an emerging depressive illness. The decision also took account of the patient's persistent insomnia, which was distressing to him. Mirtazapine can improve insomnia without the risks of tolerance and dependence seen with benzodiazepines and Z-drugs.¹⁸ Its use as a hypnotic is an off label indication and its effects appear due to antagonism at serotonergic 5-HT_{2A} receptors and histamine receptors.¹⁹

OUTCOME AND FOLLOW-UP

Psychiatric review, conducted by a consultant psychiatrist, the day after the patient first disclosed his delusions showed continuing paranoid delusions about the police and ambulance service but the next day his psychotic symptoms had resolved. The total duration of his psychotic symptoms, including his probable auditory hallucinations, had been 7 days. Two days after his delusions resolved, lorazepam was stopped as his anxiety had lessened. However, it was a further week before his anxiety fully resolved; its persistence appeared to partly reflect his PCR test remaining positive, a factor that delayed his discharge. He was discharged home from hospital 3.5 weeks after he had first presented to hospital by ambulance. At the time of discharge, he was free of anxiety, depressive and psychotic symptoms, his CRP had returned to normal (<5.0 mg/L) and he had full insight accepting that he had had a psychiatric illness related to the stress of his COVID-19 diagnosis. His discharge medication was risperidone 1 mg two times a day and mirtazapine 30 mg nocte.

Three weeks after discharge from hospital, he made a decision to stop risperidone and mirtazapine as he felt well; he had taken both medications for approximately 4 weeks. He returned to work and coped well with this. At the time of writing, he has remained well with no recurrence of psychotic or affective symptoms since he stopped medication 3 months earlier. He continues to receive follow-up by the psychiatric department and finds this reassuring.

DISCUSSION

The most likely DSM-5 diagnosis was BPD with marked stressor(s) (ie, brief reactive psychosis).¹⁶ The primary stressor appeared to be his anxiety about his health following his positive PCR test. He searched the internet and social media for COVID-19 reports, telephoned friends and family for reassurance and attended hospital by ambulance. Despite his mild physical symptoms, and the reassurance that he received from staff in quarantine and then in hospital, he continued to worry he may die. It is notable that he presented at the end of May, near the height of the pandemic in Qatar. The number of new daily cases had increased dramatically in the preceding month and peaked on 30th May. At that time, public knowledge about COVID-19 was less than it is now and anxiety was higher. Admission to a quarantine facility is likely to have been a further stressor.⁸ Quarantine, especially in a government facility rather than at home, involves enforced isolation, lack of exercise and feelings of being trapped; all are likely to foster the development of anxiety, depression and paranoid

ideation. His delusions appeared after his transfer from quarantine back to hospital; during the transfer, he temporarily lost his telephone, which added to his isolation. The patient recalled that his psychiatric symptoms led to negative comments from some colleagues and friends (see ‘patient perspective’); mental health stigma is a significant problem in the Middle East as elsewhere.²⁰ There was no evidence of stressors unrelated to COVID-19. The patient had experienced anxiety about his health 7 years earlier suggesting some diathesis to increased health-related anxiety.

We believe that the main value of this case is that it supports the view that a diagnosis of COVID-19 can precipitate psychosis, in vulnerable individuals, through health anxiety and the stress of quarantine. The patient had minimal physical symptoms of COVID-19 and several potential causes of psychosis were absent (ie, no use of propsychotic drugs, no comorbid medical disorder, no evidence of non-COVID-19 social stressors, minimal previous psychiatric history, no substance misuse). In contrast, in some case reports of COVID-19-associated psychosis, it is difficult to tease out the relative importance of potential aetiological factors. For example, Correa-Palacio *et al*⁷ reported a patient with an episode of affective psychosis occurring immediately after treatment for COVID-19 but highlighted the difficulty of identifying the precise diagnosis, which included a corticosteroid-induced psychosis, psychosis induced by hydroxychloroquine and antivirals, a contribution from the patient’s occasional cocaine use and the potential effect of neuroinflammation or direct virus neurotropism. In some case reports, psychosocial stress related to COVID-19 infection does not appear to be a significant precipitant of psychosis. For example, COVID-19-related concerns were absent or minimal in three asymptomatic COVID-19 patients who developed new-onset psychosis reported from New York³ and a further case of psychosis in a patient with mild COVID-19 disease reported from North Carolina.⁵ This variation highlights that different mechanisms may cause psychosis in patients with COVID-19 and that individual psychiatric assessment is required to devise appropriate management.

Although the patient’s psychotic episode appeared largely reactive to psychosocial stress, the possibility that organic factors may have contributed requires consideration. Immune mechanisms have been implicated in the pathogenesis of psychiatric disorders including schizophrenia²¹ and COVID-19 is associated with inflammation.¹³ The patient’s CRP and ferritin, peripheral inflammatory markers, were both elevated during his illness making it possible that inflammatory processes were involved. The elevated CRP was recorded shortly before he became psychotic and contrasted to normal assays at admission and discharge and during his period of psychosis. Other blood inflammatory markers were not measured. The patient had anosmia, a common symptom of COVID-19, that may reflect viral invasion of the olfactory neurons.²² This provides a theoretical route for transsynaptic viral entry to the central nervous system (CNS). However, as already discussed, the patient had no signs of encephalitis and so direct viral involvement of the CNS seems improbable.

BPD is a rare disorder and so research is limited. The closest diagnostic category in the 10th revision of the International Classification of Mental and Behavioural Disorders is Acute and Transient Psychotic Disorder (ATPD).²³ This allows a symptom duration of up to 3 months versus 1 month for DSM-5 BPD but the two are broadly concordant.²⁴ ATPD is two times as common in women than men.²⁵ It is more common in migrants²⁶ and in developing countries compared with developed countries.²⁵ The latter is relevant as the patient had moved to Qatar from South East Asia.

The rarity of BPD means that there is lack of evidence to guide clinical management and treatment is largely based on extrapolating from that used in schizophrenia. In practice, the treatment of BPD usually comprises psychological support and low-dose antipsychotic medication, with benzodiazepines being used if anxiety symptoms are prominent.^{27–28} First-episode psychosis responds to lower doses of antipsychotic medication than recurrent schizophrenia.²⁹ This point aside, it is good practice to use the lowest effective dose of benzodiazepine and antipsychotics in patients with COVID-19 because of the increased potential for medication side effects and drug interactions in the physically ill. There is insufficient evidence to give an evidence-based recommendation on the optimal duration of antipsychotic treatment in BPD. A recent review suggested that patients with a first episode of BPD, and no prior history of psychosis or affective disorder, should continue medication for 1–3 months after symptom remission.²⁸ The risk of psychotic recurrence at 2 and 3 years is significantly less following a first episode of BPD/ATPD versus a first episode of schizophrenia.²⁵ Nevertheless, some patients experience a further episode of BPD/ATPD and a significant proportion undergo a diagnostic shift to schizophrenia of affective psychosis.^{30–31} Given these factors, the challenges in identifying the precise aetiology of psychosis in COVID-19 patients and the lack of knowledge about the long-term neuropsychiatric consequences of COVID-19, we recommend long-term psychiatric follow-up of patients who experience a first psychotic episode associated with COVID-19.

Patient’s perspective

I was seeing excessive Facebook posts where people were saying if you get Corona you will die. Other people around me started to get Corona but when I got it and was sent to quarantine, I took it to heart, could not cope, and felt depressed. I was frightened that this is it and I am going to die. Being away from family was a big factor and I thought I am never going to be able to see them again. I started to worry about my health and after seeking initial help I got convinced that police were coming after me and would arrest me. This was very frightening as I did not even want to leave the hospital believing they are waiting for me to get discharged. I was also so disappointed to see that at the time of my illness all my friends and colleagues started to judge me and call me mad. However, I got excellent care, thank you so much to the team who looked after me. I am doing well now and friends and colleagues are now getting along well with me.

Learning points

- ▶ First episode psychosis has been reported in patients with COVID-19.
- ▶ Psychosis associated with COVID-19 may be reactive to the psychosocial stress of infection, reflect organic factors related to the disease/treatment, be multifactorial or coincidental.
- ▶ Brief reactive psychosis can occur irrespective of the severity of COVID-19 physical symptoms and quarantine may be a particular stressor.
- ▶ Psychological support and low dose antipsychotic treatment are the main treatments for brief psychotic disorder.
- ▶ Long term psychiatric follow-up is recommended following a first psychotic episode associated with COVID-19, primarily due to the risk of recurrence and diagnostic shift.

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