

# Delirious mania in a patient with COVID-19 pneumonia

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## SUMMARY

Delirious mania (the coexistence of delirium and mania) is described in the literature but not recognised in standard nosologies. We report a woman in her late 30s, with no psychiatric history, who presented with concurrent symptoms of mania and delirium. She was diagnosed with COVID-19 pneumonia (positive reverse transcription-PCR test). There was no history of substance misuse or concurrent medical illness. CT head scan was normal as were blood investigations, other than elevated inflammatory markers. She received standard treatment for COVID-19 pneumonia and lorazepam and quetiapine to treat her neuropsychiatric symptoms. She made a full recovery after 9 days. She was apyrexial with normal oxygen saturation throughout her illness. The case shows that severe neuropsychiatric symptoms can complicate otherwise mild COVID-19 pneumonia with neuroinflammation being a possible mechanism. A diagnosis of delirious mania appears to better capture the complexity of the presentation than a diagnosis of mania or delirium alone.

## BACKGROUND

COVID-19 is caused by SARS-CoV-2. It was declared a pandemic by the WHO in March 2020.<sup>1</sup> Common symptoms of COVID-19 are fever, dry cough, fatigue and myalgia. The disease primarily affects the respiratory system but multiple organs and systems can be involved including the cardiovascular system, gastrointestinal system and central nervous system.<sup>2</sup> Delirium is a well-recognised complication of COVID-19, particularly in people who are older, have more severe illness and are managed in intensive care units.<sup>3</sup> Mania/hypomania has been documented in association with COVID-19 through case reports,<sup>4 5</sup> and case series.<sup>6</sup> A health record cohort study reported an increased incidence of neuro-psychiatric disorders in the 6 months following COVID-19 diagnosis, compared with the incidence following other health conditions, with nearly one-third of patients with COVID-19 receiving a neuro-psychiatric diagnosis.<sup>7</sup> An increased incidence, both overall and first episode, was seen as for most individual neuropsychiatric diagnoses, including mood disorders and first onset psychosis (data were not reported for mania alone).<sup>7</sup>

COVID-19 can cause psychiatric syndromes through multiple mechanisms. These include respiratory and metabolic disturbances secondary to the disease affecting peripheral systems, neuroinflammation, possible neurotropism of SARS-CoV-2, abnormalities in coagulation and iatrogenic effects,

for example, the effect of exogenous corticosteroids.<sup>8</sup> Psychosocial stressors associated with infection, including fear and social isolation, are a further aetiological pathway.<sup>9</sup> In addition, in any individual case, the association of psychiatric illness with COVID-19 may be coincidental with the psychiatric episode reflecting another cause, for example, substance misuse or an underlying bipolar disorder in the case of mania.

Traditionally mania and delirium are seen as separate syndromes. However, the combination of mania and delirium, so called delirious mania, has a long history. It was first reported by Calmiel,<sup>10</sup> and then by Bell,<sup>11</sup> hence, the eponymous term Bell's mania. It has been reported regularly since, though only in case reports or small case series.<sup>12</sup> This may partly reflect its absence as a diagnostic category in current nosologies; delirious mania does not appear in either the Diagnostic and Statistical Manual of Mental Disorders (5th edition) (DSM-5),<sup>13</sup> or the International Classification of Diseases (10th edition) (ICD-10).<sup>14</sup> Its incidence is unclear. Some regard it as a rare syndrome but others have suggested that up to 20% of patients with acute mania show some signs of delirium and that delirious mania warrants specific identification in the diagnostic nomenclature.<sup>15 16</sup> Some authors restrict delirious mania to a syndrome that occurs without an identified organic cause; such cases have been reported in individuals with a history of bipolar disorder<sup>17</sup> and in those without any prior psychiatric diagnosis.<sup>15</sup> This form of delirious mania has been suggested to be related to lethal catatonia and to be responsive to electroconvulsive treatment (ECT) and benzodiazepines.<sup>15 17</sup> Others have taken a broader view of delirious mania and included cases that appear secondary to medical disorders and medication.<sup>18–20</sup> The syndrome has an acute onset and autonomic instability and hyperpyrexia occur in some but not all cases.<sup>12</sup>

We report a case of delirious mania associated with otherwise mild COVID-19 pneumonia. The patient did not require intubation and was apyrexial and had normal oxygen saturation throughout her illness. The only abnormalities on extensive investigations were chest X-ray (CXR) changes consistent with pneumonia and raised peripheral inflammatory markers. The case is relevant for several reasons. Delirious mania is rarely reported in the literature with only one previous case documenting its association with COVID-19.<sup>21</sup> A further report described a patient presenting with a first manic episode 2 days after discharge from hospital following treatment for COVID-19 pneumonia and delirium.<sup>22</sup> Although the patient did not experience



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concurrent symptoms of mania and delirium (ie, the core diagnostic feature of delirious mania), the close temporal relationship of both syndromes suggests the possibility of a common pathophysiology in that case.<sup>22</sup> The case we report adds to the literature on delirious mania and suggests that it is part of the range of neuropsychiatric disorders that can occur in COVID-19. It also illustrates that severe neuropsychiatric disorders can occur in individuals with otherwise relatively mild COVID-19. Finally, the details suggest neuroinflammation as a possible pathophysiological mechanism.

### CASE PRESENTATION

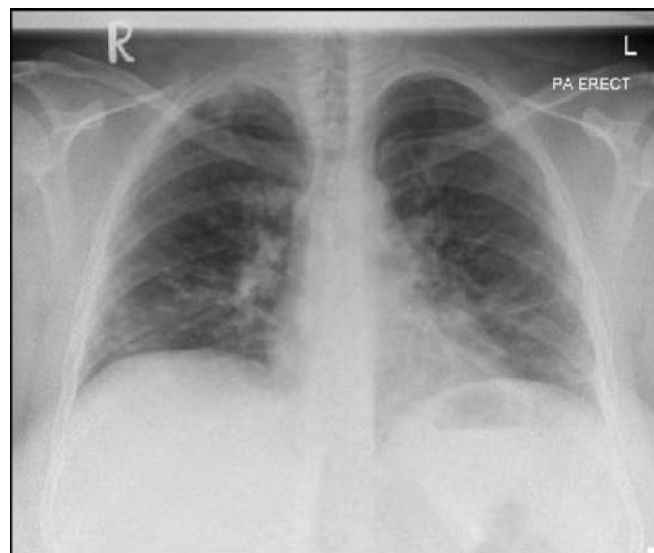
A woman in her late 30s developed a mild cough and diffuse bodily aches and attended for a COVID-19 test (reverse transcription PCR (RT-PCR)). The test was positive, she was advised to home quarantine but no specific treatment was commenced given her mild symptoms. The patient was not worried by the COVID-19 diagnosis given her mild symptoms. Four days later a relative, with whom she lived, brought her to the emergency department (ED) at a major hospital. The relative had become increasingly concerned about her behaviour and reported that since her diagnosis 4 days earlier she had been agitated, required less sleep and had been talking excessively. In addition, she had appeared confused, talking to people who were not there (suggesting she was responding to hallucinations), calling family members by the wrong name and on one occasion taking her clothes off for no reason. On the day of admission, she impulsively drank 100 mL of body wash which was the final factor leading her relative to bring her to hospital. The patient reported a mild cough and loss of taste but no other physical symptoms. She had no vomiting, abdominal pain or related symptoms and no medical intervention was deemed necessary for the ingestion of the body wash.

She had no family history of mental health problems. She had no current or past physical health disorders. She was not taking any regular medication, either prescribed or over the counter. She was a non-smoker and had never drunk alcohol or used illicit substances. She had a supportive relationship with her family.

Physical examination revealed bilateral basal crepitations but was otherwise normal. Her vital signs were normal; temperature 36.8°C (tympanic), respiratory rate 15 per minute, pulse 71 per minute, blood pressure: 118/71 mm Hg, SpO<sub>2</sub>: 98% on room air.

At presentation she was briefly tearful, highly agitated and kept wandering in the department and asking to go home. Her agitation required sedation with intramuscular haloperidol. Based partly on the results of a CXR (see the next section), a diagnosis of COVID-19 pneumonia was made. She was referred to the consultation liaison (CL) psychiatry team for advice on her psychiatric symptoms. When seen by the psychiatrist, she reported being happy and wanting world peace. Although she had slept poorly for several days, she was not tired. She had grandiose religious ideas believing she had a special 'spiritual power' from God that she could give to others. Her family confirmed that these ideas were out of keeping with her normal beliefs. She was embarrassed about drinking the body wash prior to admission and explained her actions by saying she had liked its smell and taste. She denied that it had been an attempt to harm herself.

On mental state examination, she was overactive, her speech was pressured and she showed flight of ideas. Subjectively she reported being happy. Objectively her mood was elated and labile. Her grandiose religious ideas have already been referred to. She had a short attention span. She was alert and orientated



**Figure 1** Chest X-ray on admission.

in place and person but not time. She had limited insight into her condition; she accepted she had COVID-19 but was not convinced she was psychiatrically unwell. With persuasion she agreed to remain in hospital and receive treatment from the medical and psychiatric teams.

### INVESTIGATIONS

Investigations conducted on admission showed a positive SARS-CoV-2 RT-PCR test and raised inflammatory markers; C reactive protein 77 mg/mL (normal reference ranges: <5 mg/L), ferritin 274 µg/L (normal reference range: 12–160 µg/L), lactate dehydrogenase 477 U/L (normal reference range: 135–214 U/L). CXR, on admission, showed bilateral lower zone patches of ground glass opacities/atelectatic bands (figure 1). Opinions differ on the optimal chest imaging for patients presenting with suspected COVID-19 pneumonia.<sup>23</sup> In this case, the decision to use CXR, rather than high-resolution CT (HRCT) scan thorax, was based on PCR having already confirmed the diagnosis of COVID-19 and there being no plausible differential diagnosis. Furthermore CXR is cheaper, involves a lower dose of radiation and is a quicker procedure for the patient than HRCT; the latter is a particular advantage in an agitated patient. All other investigations on admission were normal; this included CT head scan, ECG, thyroid function tests, blood chemistry, coagulation screen, interleukin 6, pregnancy test and paracetamol and salicylate levels (table 1). Blood tests were repeated on day 3 and day 4 of the admission and were normal other than inflammatory markers which showed a further increase from admission to day 3 (table 1).

### DIFFERENTIAL DIAGNOSIS

The primary diagnosis made by the medical team was straightforward; the patient had COVID-19 pneumonia. Her respiratory symptoms were mild throughout her illness that is, she did not have fever, tachypnoea, respiratory distress or an SpO<sub>2</sub> <90% on room air. The psychiatric diagnosis was more challenging. The patient showed features of both delirium and mania at presentation that continued during her inpatient stay (see the next section for a description of symptoms during the inpatient admission). In terms of manic features, she had elevated mood, decreased need for sleep, grandiose ideation, increased

**Table 1** Summary of principal investigations during admission\*

	Day 1 of admission	Day 3 of admission	Day 4 of admission
<b>Vital signs</b>			
Temperature (°C)	36.8	36.4	36.9
Pulse/BP (bpm/mm Hg)	71, 118/71	78, 117/60	73, 107/65
Respiratory rate (br/min)	15	18	18
Oxygen saturation (%)	98 (room air)	98 (on 2 L/min oxygen via nasal cannula)	95 (room air)
<b>Haematology</b>			
White cell count ( $\times 10^9$ /L)	5.2	4.8	–
Absolute neutrophil count ( $\times 10^9$ /L)	3.8	4.0	–
Red blood count ( $\times 10^{12}$ /L)	4.7	4.6	–
Haemoglobin (g/L)	117	124	–
Platelets ( $\times 10^9$ /L)	307	299	–
<b>Blood chemistry</b>			
Urea (mmol/L)	2.4	2.4	–
Creatinine (mmol/L)	70	58	–
Sodium (mmol/L)	138	137	–
Potassium (mmol/L)	3.6	3.5	–
Chloride (mmol/L)	101	–	–
Bicarbonate (mmol/L)	25	–	–
Alk phosphatase (U/L)	60	69	–
AST (U/L)	34	29	23
ALT (U/L)	28	23	36
<b>Endocrinology</b>			
T4 ( $\mu$ g/L)	14.2	–	–
TSH ( $\mu$ g/L)	1.55	–	–
<b>Inflammatory markers†</b>			
Ferritin ( $\mu$ g/L)	274	344	316
C reactive protein (mg/L)	77	105	55
Lactate dehydrogenase (U/L)	477	515	450
<b>Coagulation screen</b>			
Prothrombin time (s)	13.8	–	–
INR	1.2	–	–
APTT (s)	27.5	–	–
<b>Serology</b>			
Hepatitis B surface antigen	Negative	–	–
Hepatitis C antibody	Negative	–	–
HIV Ag/Ab combo	Negative	–	–
COVID-19 PCR	Positive	–	–
<b>Miscellaneous</b>			
CT head scan	Normal	–	–
ECG	Normal	–	–
CXR	Bilateral lower zone patches with ground glass opacities/atelectatic bands	–	–

Continued

**Table 1** Continued

	Day 1 of admission	Day 3 of admission	Day 4 of admission
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\*The only abnormalities were the chest X-ray, positive COVID-19 PCR and raised inflammatory markers.

†Normal reference range: ferritin 12–160  $\mu$ g/L; C reactive protein <5 mg/L; lactate dehydrogenase 135–214 U/L.

ALT, alanine aminotransferase; APTT, activated partial thromboplastin time; AST, aspartate aminotransferase; BP, blood pressure; CXR, chest X-ray; INR, international normalised ratio; TSH, thyroid stimulating hormone.

talkativeness, pressured speech, flight of ideas and distractibility. She also showed classic features of delirium, namely an acute disturbance of attention, awareness and cognition.<sup>13</sup> Symptoms within these domains included misidentification of family members, brief visual hallucinations, reduced attention, disorientation to time and behaviours that implied reduced awareness including undressing inappropriately and ingesting body wash. Her neuropsychiatric syndrome required hospital admission and lasted 9 days in total. The presence of concurrent symptoms of mania and delirium led to a diagnosis of delirious mania. This appeared to better capture the complexity of the presentation than a diagnosis of mania or delirium alone which would only explain some of the symptoms.

Based on psychomotor features, delirium is traditionally subdivided into hyperactive, hypoactive and mixed types. The hyperactive form appears most common in younger adults with COVID-19 whereas the hypoactive form appears more common in elderly patients.<sup>24</sup> Although the patient showed some symptoms consistent with hyperactive delirium, the presence of manic symptoms is not explained by delirium. Her symptoms did not show a diurnal variation, a common feature of delirium, and her disorientation was relatively mild. We considered, and rejected, a diagnosis of brief psychotic disorder. In DSM-5 this is a psychotic disorder that lasts between 1 day and 1 month and is followed by full recovery.<sup>13</sup> The diagnosis was rejected as it does not adequately account for symptoms of delirium or mania and furthermore psychotic symptoms were not the most prominent part of the patient's presentation.

Irrespective of the precise psychiatric diagnosis (mania, delirium or delirious mania), the time course of the patient's psychiatric symptoms strongly implicates COVID-19 as the cause. Her psychiatric symptoms started soon after she developed physical symptoms of COVID-19 (ie, bodily aches and a cough) and received a positive PCR test. The duration of symptoms (9 days in total) is consistent with COVID-19. The raised inflammatory markers provide a plausible aetiological mechanism by which COVID-19 could cause neuropsychiatric symptoms. COVID-19 is a recognised cause of delirium<sup>3,6</sup> and has also been reported in association with mania.<sup>4–6</sup> Psychosocial stress did not appear relevant to the onset of the psychiatric disorder. The patient was not alarmed by her initial COVID-19 diagnosis and she was required to quarantine at home rather than at a government approved quarantine facility.

Causes for her neuropsychiatric illness other than COVID-19 were considered and rejected. In terms of organic causes, she had no concurrent physical illness and investigations other than the CXR and raised inflammatory markers were normal. This included a normal CT head scan. She had never used illicit drugs or alcohol, excluding a drug-induced aetiology. Certain medications, including corticosteroids, antibiotics, thyroxine and antidepressants, can cause mania.<sup>25</sup> However, the patient did not

receive any medications, prescribed or over the counter, prior to the onset of her illness ruling out a medication related aetiology.

We considered the possibility that the association of delirious mania with COVID-19 was coincidental with the former representing a first episode of bipolar disorder. This cannot be totally excluded but is made less likely by the patient's age and the absence of a family history of bipolar disorder. The patient was in her late 30s and this was her first episode of psychiatric illness. In contrast, the mean age of onset of bipolar 1 disorder is 26 years,<sup>26</sup> and nearly two-thirds of people diagnosed with bipolar 1 disorder have a family history of affective illness.<sup>26</sup> It is recommended that the first onset of manic symptoms in mid-life or later should prompt consideration of organic causes.<sup>13</sup>

## TREATMENT

The patient remained an inpatient for 5 days. She was commenced on a standard treatment protocol for COVID-19 pneumonia including parenteral dexamethasone, ceftriaxone, enoxaparin (for venous thromboembolism prophylaxis) and remdesivir. She received oxygen therapy via a nasal cannula (2L/min) on day 3 of the admission; this was a precautionary measure influenced by the fact that her inflammatory markers had risen further since admission. Throughout the 5-day admission her vital signs, including pulse, blood pressure, oxygen saturation and temperature, were normal.

There was close collaborative working between the medical and CL psychiatry teams while following strict infection control measures. She was reviewed daily by a consultant psychiatrist with additional assessments from psychiatric nurses in the CL team. She was commenced on oral lorazepam 1 mg two times per day to control agitation and simultaneously started quetiapine to treat the symptoms of delirium and mania. Quetiapine was rapidly titrated to 150 mg two times per day. She was initially nursed on one to one nursing observations due to her vulnerability and unpredictable behaviour. She was provided with support and reassurance regarding COVID-19 and later in the admission with psychoeducation. Regular video call communication with her family was facilitated.

For the first few days after admission she remained unpredictable in her behaviour, overactive and showed elated, irritable and labile mood. For example, on one occasion she was observed singing and telling jokes to staff and soon after being tearful. Her speech remained pressured. The day after admission she washed her clothes in a toilet but was unable to explain her actions. On another occasion she reported brief visual hallucinations, seeing birds on the ward when there were none there. By day three of admission, her mental state was improving and by day five it had returned to normal and her SARS-CoV-2 PCR test was reported as reactive. After discussion with her family she was discharged home with a follow-up appointment. The patient and her family were advised to contact the psychiatric team, or to attend the ED, if there were any signs of a relapse or if her mental state changed in any other significant way. Prior to discharge her lorazepam had been gradually reduced and stopped. Her discharge medication was quetiapine 150 mg two times per day.

## OUTCOME AND FOLLOW-UP

The patient has remained well since discharge from inpatient care with no evidence of any psychiatric symptoms. Psychiatric follow-up has been conducted by telephone in keeping with local pandemic protocols. The patient was initially reviewed 2 weeks after discharge and reported that she was well. She reflected on how ill she had been from a psychiatric view point during her

admission. Her quetiapine was reduced from 150 mg two times per day to 200 mg at night-time as she reported daytime sedation. Her quetiapine was gradually withdrawn during a series of further telephone appointments and finally stopped 4 months after discharge from inpatient care. At the time of writing she has taken no psychiatric medication for several months.

## DISCUSSION

The patient was relatively young and delirious mania complicated otherwise mild COVID-19 pneumonia. In contrast, a study of consecutive patients admitted to hospital in Italy with COVID-19 showed that those with delirium differed from those without delirium by being older (mean age 82 years), having a lower  $PO_2/FiO_2$  and a higher prevalence of neuropsychiatric comorbidities, specifically dementia and epilepsy.<sup>27</sup> The reported case highlights that COVID-19 should be considered as a potential diagnosis in patients who present with a first episode of mania or delirium, even if physical symptoms of COVID-19 are absent or not prominent.

The elevated peripheral inflammatory markers support neuroinflammation as a possible mechanism for COVID-19 causing the patient's neuropsychiatric symptoms. Inflammatory processes have been implicated in a wide range of psychiatric disorders including bipolar disorder, schizophrenia, depression and delirium.<sup>28–30</sup> Pro-inflammatory cytokines have been shown to be elevated, and anti-inflammatory cytokines reduced, in bipolar patients, particularly during manic and depressive phases, compared with controls.<sup>31</sup> Inflammation may trigger psychiatric illness by disrupting the blood brain barrier (BBB), neurotransmitter systems and microglial function.<sup>32</sup> BBB dysfunction may also allow SARS-CoV-2 to enter the central nervous system. The virus may also infect macrophages and monocytes in the periphery which then cross the BBB. It is unclear to what extent SARS-CoV-2 is neurotropic but this provides a further potential route for neuroinflammation.<sup>33</sup>

The anecdotal nature of the literature on delirious mania means there is limited evidence to guide management. Contributing organic causes need to be treated/reversed as with any case of delirium or organic mania.<sup>25</sup> Previous reports of delirious mania support the use of a second generation antipsychotic and a mood stabiliser in combination,<sup>17</sup> or high dose benzodiazepines,<sup>34</sup> or ECT.<sup>15 17 21</sup> First generation antipsychotics appear less effective than second generation antipsychotics in treating delirious mania, and may even lead to a worsening, and are not recommended.<sup>15 34</sup> ECT appears effective when catatonic features and marked excitement are present.<sup>15 17 21</sup> In our case, COVID-19 pneumonia was treated according to a standard protocol and a second generation antipsychotic and a low dose benzodiazepine were prescribed to treat the episode of delirious mania. This regimen appeared effective, though one cannot exclude the possibility that the syndrome would have resolved spontaneously without pharmacological treatment. Antipsychotics are a first line treatment for acute mania and short-term adjunctive benzodiazepines are often used to treat associated insomnia and agitation.<sup>35</sup> Antipsychotics are also widely used to manage agitation and psychotic features in hyperactive delirium when non-pharmacological interventions alone have proved ineffective. However, the efficacy of antipsychotics in delirium remains uncertain.<sup>36</sup> The optimal duration of antipsychotic treatment following resolution of both organic mania and delirious mania is unclear and best decided on an individual basis in discussion with the patient. Treatment duration will partly be influenced by whether antipsychotic side effects occur. Patients

should continue to have their mental state monitored after anti-psychotics are withdrawn because of the possibility of relapse. Long-term studies of patients with neuropsychiatric disorders associated with COVID-19 are necessary to determine the prognosis and guide future management.

### Learning points

- ▶ Delirious mania (ie, the coexistence of symptoms of delirium and mania) has a long history but is not recognised in standard nosologies. We report an apparent case of delirious mania associated with COVID-19.
- ▶ Delirious mania can complicate otherwise mild COVID-19 pneumonia. COVID-19 should be considered as a potential diagnosis in patients who present with mania, delirium or delirious mania, especially if this is a first episode.
- ▶ A combination of quetiapine, a second generation antipsychotic, and low dose lorazepam appeared effective in treating delirious mania.
- ▶ Neuroinflammation is a possible mechanism for COVID-19 associated delirious mania.
- ▶ Long-term studies of patients with neuropsychiatric morbidity associated with COVID-19 are necessary to determine the long term prognosis and guide future management.

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