


# First Episode, Late-Onset Organic Mania During the Convalescence Phase of COVID-19: Case Series and Literature Review

Ranganath R. Kulkarni<sup>1</sup> , Aditya A. Pandurangi<sup>1</sup>, Swapna A. Pandurangi<sup>1</sup>, Raghavendra C. Patil<sup>1</sup> and Divyashree N. S.<sup>1</sup>

COVID-19 is an acute respiratory infection caused by severe acute respiratory syndrome coronavirus type 2 (SARS-CoV-2). It also presents with multisystemic involvement, including the cardiovascular system, gastrointestinal system, and central nervous system (CNS), the latter presenting with neuropsychiatric manifestations, including delirium.<sup>1</sup> SARS-CoV-2 appears to have a distinct neurotropic property that can potentially breach the blood-brain barrier, infiltrate the CNS, and influence neuro-immune interactions via macrophages, microglia, and astrocytes, leading to both acute and long-term neuropsychiatric sequelae.<sup>2,3</sup>

Clinical trials<sup>4,5</sup> have found patients with COVID-19-related pneumonia at-risk for neurological (stroke, encephalopathy, encephalitis, delirium, and Guillain-Barre syndrome) and psychiatric (depression, anxiety, insomnia, psychosis, and post-traumatic stress disorder) disorders that can occur before or after the appearance of respiratory signs.<sup>6</sup> Furthermore,

steroids, chloroquine, hydroxychloroquine (HCQ), and other COVID-19 treatments can complicate clinical scenarios because of potential neuropsychiatric side-effects such as psychosis, mood disorders, and suicide risk, necessitating timely psychiatric evaluation and interventions.<sup>7,8</sup> We present a case series of first-episode, late-onset organic mania during the convalescence phase of COVID-19.

## Case 1

A 70-year-old married male, literate, and self-employed, presented to the emergency department with acute onset, first episode, progressive course of illness characterized by persistent and pervasively elevated mood, increased speech, increased goal-directed activity, reduced need for sleep, irritability, overfamiliarity, and over-religiosity for two weeks. He had a history of being treated for COVID-19 two weeks prior to the onset of the first psychiatric symptom, with a daily parenteral dose of ceftriaxone 2 gm and dexamethasone

8 mg, administered for initial five days along with oral medicines such as HCQ 400 mg, oseltamivir 75 mg, azithromycin 1000 mg, acetaminophen 1000 mg, and vitamin-C 1500 mg. A family history of psychosis in his younger sister was noted. There was no history of significant medical or psychiatric illnesses or substance abuse at any time. General physical examination and systemic (including CNS) examination revealed no significant abnormality. Mental status examination revealed increased psychomotor activity, pressured speech, grandiose delusion, elated mood, impaired judgment, and absent insight. He received a clinical diagnosis of organic manic disorder (Fo6.30) as per the *International Classification of Diseases*, tenth revision (ICD-10) diagnostic criteria.

On admission, his Hindi Mental Status Examination score was 29/31, screening out cognitive decline. Young Mania Rating Scale (YMRS) score was 31/60 (moderate severity), and the Brief Psychiatric Rating Scale score was 32/126. Except for an

<sup>1</sup>Dept. of Psychiatry, Dharwad Institute of Mental Health and Neurosciences, Dharwad, Karnataka, India.

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**Address for correspondence:** Ranganath R. Kulkarni, Dept. of Psychiatry, Dharwad Institute of Mental Health and Neurosciences, Dharwad, Karnataka 580008, India. E-mail: dranantoo7@rediffmail.com

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elevated erythrocyte sedimentation rate of 110 mm at the end of the first hour, his blood investigations revealed normal complete blood count, serum electrolytes, liver and renal profiles, and nonreactive retroviral and hepatitis-B antigen tests. Magnetic resonance imaging of the brain revealed mild diffuse cerebral atrophy, with old lacunar infarcts in bilateral basal ganglia and discrete areas of hyperintensities in bilateral centrum semiovale, suggesting small vessel ischemic white matter lesions. High-resolution computed tomography (HRCT) of the chest revealed mild residual changes of viral bronchopneumonia in both lungs. Cerebrospinal fluid (CSF) analysis revealed elevated proteins (79.87 mg/dL), with normal cell count (2 cells/cu.mm, all lymphocytes), sugar (61.43 mg/dL), adenosine deaminase (6.9 IU/L), and lactate dehydrogenase (30.0 IU/L) within normal range. CSF for SARS-CoV-2 antigen using reverse transcriptase-polymerase chain reaction (RT-PCR) test was also negative. He showed clinical improvement in four weeks (Brief Psychiatric Rating Scale = 18/126; YMRS = 2/60) to a daily dose of olanzapine 10 mg, trihexyphenidyl 2 mg, and diazepam 5 mg, with good compliance and no side-effects.

## Case-2

A 45-year-old married male, literate, and self-employed, presented with acute onset, first episode illness with a progressive course, characterized by persistent and pervasively elevated mood, increased speech, increased goal-directed activity, reduced need for sleep, irritability, over-religiosity, suspiciousness, and disinhibited behavior for four weeks. He had COVID-19 three weeks prior to the onset of the first psychiatric symptom. He had recovered with an oral daily dose of azithromycin 500 mg, vitamin-C 1500 mg, and acetaminophen 1000 mg given for the initial five days. He had no past or family history of medical or psychiatric illnesses or substance abuse. General physical examination and systemic (including CNS) examination revealed no significant abnormality. Mental status examination revealed increased psychomotor activity, delusions of grandiosity and reference, elated mood, impaired judgment, and absent insight. He received a clinical diagnosis of organic manic disorder (F06.30) as per ICD-10 diagnostic criteria.

On admission, the YMRS score was 39/60, suggesting severe mania. Blood

investigations revealed normal complete blood count, serum electrolytes, liver and renal profiles, D-dimer, and C-reactive protein, with nonreactive retroviral and hepatitis-B antigen tests. Magnetic resonance imaging brain and HRCT of the chest were normal. CSF for SARS-CoV-2 antigen using RT-PCR could not be done because of dissent by the patient for lumbar puncture. He showed clinical improvement in four weeks (YMRS = 2/60), with a daily dose of T. sodium valproate 600 mg, risperidone 4 mg, trihexyphenidyl 2 mg, and lorazepam 2 mg, with good compliance and no side-effects.

## Discussion

Literature on the neurological and psychiatric complications of COVID-19 is emerging, with most being individual cases or case series.<sup>9</sup> Neuropsychiatric manifestations during active COVID-19, such as new-onset, nonaffective psychosis in three COVID-19 patients without typical COVID-19-related anosmia, ageusia, respiratory or gastrointestinal symptoms;<sup>10</sup> severe paranoia leading to suicide attempt with no prior psychiatric history;<sup>11</sup> and acute mania with normal neuroimaging and negative SARS-CoV-2 antigen in CSF sample;<sup>12</sup> have been reported. However, neuropsychiatric manifestations of COVID-19 during the convalescence phase are less reported, with the first such case being first episode mania occurring after three weeks of recovery from COVID-19, with positive SARS-CoV-2-specific immunoglobulin-G antibody and negative RT-PCR for antigen in CSF.<sup>13</sup> Another reported case is of new-onset delusional parasitosis occurring after four weeks of recovery from COVID-19.<sup>14</sup> Although a few cases have been reported with positive CSF for SARS-CoV-2 antigen/antibody, our first case had negative RT-PCR for SARS-CoV-2-specific antigen in CSF sample as he presented during the convalescence phase, three weeks after recovery from acute COVID-19. This could also be because of differences in the sampling techniques, CSF antigen detection tests, cycle-threshold criteria, and time at which the test is performed; low sensitivity of tests (false-negative results); absence of viral antigen in CSF sample; early CSF clearance; or low CSF viral titer.<sup>9</sup> In addition, the SARS-CoV-2 antigen in CSF may be detected during the early stages of COVID-19, especially when the viral load

is high than during the convalescence phase.<sup>15,16</sup> Hence, negative CSF RT-PCR for SARS-CoV-2 antigen, especially during the convalescence phase, does not necessarily rule out the virus-related neuro-inflammatory process, as it is usually not detected in most cases.<sup>15,16</sup>

Current evidence highlights the lack of clarity about the exact origin of the neuropsychiatric manifestations of COVID-19. Multiple factors may contribute, including the systemic effects of COVID-19 (such as multi-organ dysfunction, coagulopathy, systemic inflammation or virus-associated neuro-inflammatory trigger, cytokine network dysregulation, or possible direct viral neuro-invasion)<sup>17</sup> and the COVID-19 medications.<sup>7,8</sup> In addition, hypoxia, possibly psychosocial factors like quarantine-stress related to prolonged isolation during the COVID-19 illness, and the sensational effect of mass-media triggering pandemic “neurosis” in vulnerable individuals may all have additive triggering effects on the development of psychiatric symptoms.

Corticosteroid-induced psychiatric adverse events include mania/hypomania (35%), depression (28%), and psychosis (24%). The primary risk factor is high dose of corticosteroids with lower incidence (1.3%) at dose <40 mg/day of prednisolone or its equivalent (5 mg prednisolone = 0.75 mg dexamethasone, i.e., equivalent to 53.3 mg/day in Case 1). This increases to 18.4% if the dose is 80 mg/day, with most cases developing psychiatric symptoms within the first five days (median = 11 days) of initiation of corticosteroid therapy. However, this can occur any time up to six weeks, including after completion or discontinuation of therapy.<sup>18</sup> Apart from corticosteroids, other medications used to treat COVID-19 (HCQ, azithromycin, remdesivir, oseltamivir, lopinavir/ritonavir, tocilizumab) may also induce psychiatric adverse events (3.2%), of which three-fourths (2.24%) are linked to HCQ that causes suicidal activation (50%), insomnia or anxiety (34%), psychosis (21.4%), or depression/cognitive disturbances (3.6%).<sup>8</sup>

We used the algorithm laid by Naranjo et al.<sup>19</sup> to estimate the probability of adverse drug events in our cases. In our first case, who received multiple COVID-19 medications (i.e., dexamethasone, HCQ, oseltamivir, and azithromycin), the algorithm indicated a low probability score of 1, depicting the “possible” additive role of

the suspected drugs. In contrast, our second case did not receive the above medications, except azithromycin. Of all macrolides, clarithromycin has been mostly related to neuropsychiatric adverse events like mania (antibiomania), delirium, acute psychosis, and even hallucinations; although rare, a few cases of azithromycin-induced mania in the older adults have also been reported.<sup>20</sup> In our second case, who received azithromycin, Naranjo et al.<sup>19</sup> algorithm indicated a probability score of 0, suggesting a “doubtful” role. Due to the uncertain probability of medication-related mania in our cases, ‘confident’ ICD-10 diagnosis of other specified mental disorders due to brain damage, dysfunction and physical disease (Fo6.8) is less likely.

The coincidental finding of a family history of psychosis in the first case, but not in the second case, rendered the ICD-10 diagnosis of Fo6 (general criteria) as “provisional” in the former and “confident” in the latter. However, such an association is currently unclear and warrants further evaluation for its casual or causal nature. This case series also highlights the unusual finding of the temporal relationship between COVID-19 and first episode mania during the convalescence phase supported by elevated CSF proteins and erythrocyte sedimentation rate (in one case). With the Naranjo et al.<sup>19</sup> algorithm indicating medication-related mania to be an uncertain probability, in the absence of substance abuse, excessive preoccupation about COVID-19, or attributable psychosocial stressors, this report possibly suggests that virus-related neuro-inflammatory triggers may lead to mania in vulnerable individuals.

Despite the emerging evidence supporting COVID-19-related de novo neuropsychiatric manifestations, albeit less than that of exacerbation of pre-existing psychiatric disorders during COVID-19, it is difficult to conceptualize a direct link between psychiatric conditions and the virus's neurotropic effects because of multiple factors such as poor awareness, medications used during COVID-19 therapy, hypoxia, lack of follow-up, and diathesis-stress, which are invariably involved during any biological disaster.<sup>21</sup> Hence, the possibility of multifactorial causation appears appropriate.

## Conclusion

Individuals exposed to SARS-CoV-2 need time-series surveillance of clinical-neurochemical-radiological progress of neuropsychiatric and neuro-immune sequelae. To ensure better short- and long-term recovery of COVID-19 patients, it is prudent to have a screening, intervention, and therapy strategy to prevent and decrease neuropsychiatric sequelae.<sup>9</sup> In view of emerging evidence, vigilance and a high index of suspicion of possible neuropsychiatric manifestations during the acute and convalescence phases of the COVID-19, including possible adverse drug events, are warranted.

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### ORCID iD

Ranganath R. Kulkarni  <https://orcid.org/0000-0002-9804-492X>

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