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Case Report

# COVID-19–Associated Hyperactive Intensive Care Unit Delirium With Proposed Pathophysiology and Treatment: A Case Report


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## *Introduction*

Coronavirus disease 2019 (COVID-19) was first described in Wuhan, Hubei Province, China, in December of 2019.[1] Worldwide, at the time of this publication, there have been over 4.2 million confirmed cases and over 287,000 deaths.[2] Clinical manifestations vary from asymptomatic to an acute respiratory illness with progression to respiratory distress and failure.[3] Treatment challenges in the intensive care unit (ICU) include severe acute respiratory distress syndrome (ARDS) due to severe acute respiratory syndrome coronavirus (SARS-CoV-2), cardiac and other organ dysfunction, and superimposed infections.[1,4] In addition, emerging data support a viral neuroinvasive component.[5] Mao and colleagues described numerous neurological symptoms imposing further challenges.[6] Delirium, not surprisingly, emerges as an additional significant complication and burden in these patients.

This case report details complexities in the management of hyperactive delirium associated with COVID-19 infection in the ICU. In general, delirium is associated with increased length of hospital stay, morbidity, and mortality in mechanically ventilated ICU patients.[7] However, there is a paucity of literature discussing the management and impact of delirium on patients with COVID-19.

We discuss the proposed pathophysiology of delirium associated with COVID-19 infection and provide a framework for the evaluation and management of delirium occurring in patients with SARS-CoV-2.

## *Case Description*

Ms. A, previously healthy 70-year-old woman presented to an urgent care clinic with 5 days of fever, malaise, headache, and dry cough. Chest radiography revealed right lung airspace opacities. She was prescribed azithromycin and amoxicillin/clavulanic acid. Over the next day, her shortness of breath worsened and her viral polymerized chain reaction test for SARS-CoV-2 returned positive. Ms. A then presented for a scheduled hospital admission, where she was febrile to 103.7°F and tachypneic. Absolute lymphocyte count was 710; interleukin-6, 31 pg/mL; ferritin, 1222 ng/mL; C-reactive protein, 3.4 mg/dL; and procalcitonin, 0.53 ng/mL. Renal function demonstrated impairment above her baseline (estimated glomerular filtration rate was 52 mL/min/1.73 $m^2$). Aspartate aminotransferase and alanine aminotransferase were mildly elevated at 112 and 139 units/L, respectively. Her initial corrected QT interval (QTc) was 397 ms.

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She was treated with 5 days of ceftriaxone and azithromycin because of concern for bacterial coinfection and 10 days of remdesivir as a part of trial for treatment of COVID-19. She was transferred to the ICU for worsening hypoxic respiratory failure on hospital day 3 and intubated on hospital day 4. While she was briefly extubated on day 26, she required reintubation on the same day.

To facilitate mechanical ventilation and combat significant agitation, she received numerous sedative drips, including dexmedetomidine, hydromorphone, propofol, midazolam, and ketamine, as well oxycodone (up to 60 mg daily) and chlordiazepoxide (up to 30 mg daily). Other psychotropic agents used by her primary team included quetiapine (up to 175 mg daily) and melatonin 5 mg nightly. She remained restless and agitated.

Psychiatry was consulted on admission day 29 to assist with management of agitation, 1 day before tracheostomy placement on hospital day 30. Owing to strict COVID-19 infection-control policies, she was assessed virtually, by chart review, and via discussions with her nurses, ICU team, and family. The diagnosis of delirium was made according to the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition, based on acute onset of disturbance of attention and awareness, impaired cognition, agitation, and sleep-wake cycle dysregulation in context of medical illness,[8] and confirmed by the Confusion Assessment Method for the ICU[9] and the Stanford Proxy Test for Delirium.[10,11]

Given psychiatry's recommendations, melatonin was increased to 15 mg nightly to regulate sleep-wake cycle and for the antioxidant and anti-inflammatory effects, and suvorexant, an orexin antagonist, was added at 20 mg for sleep-wake cycle regulation. Guanfacine, an alpha-2 agonist, was started at 0.5 mg twice daily and titrated to 1 mg thrice daily to reduce sympathetic outflow, manage agitation, and assist in weaning intravenous sedatives. Intravenous valproic acid (VPA; titrated to 1250 mg per day) was also started for management of agitation and symptoms of hyperactive delirium and to facilitate tapering of multiple other sedative deliriogenic medications. Quetiapine was initially titrated to 250 mg distributed throughout the day, but owing to its ineffectiveness, it was discontinued on day 3 of psychiatric consultation and instead intravenous haloperidol (titrated to 8 mg per day) was used to manage symptoms of hyperactive delirium. Of note, nursing staff was educated and asked to examine for extrapyramidal side effects of antipsychotics during their regular evaluation and care for Ms. A.

Over the following 5 days, she tolerated discontinuation of all sedative drips with gradual tapering of chlordiazepoxide (discontinued on day 6 of psychiatric consultation) and oxycodone (discontinued on day 7 of psychiatric consultation). She had ongoing medical complications, including fevers and pneumothorax, during this phase of her treatment. Regardless, her mental status continued to improve. VPA was discontinued on day 5 of consultation, and haloperidol was discontinued on day 11 of consultation. On day 10 of psychiatric consultation, she was fully cognizant, awake, alert, oriented, following simple and complex commands, communicative via the use of mouthing and writing (assessed virtually), and displayed no evidence of ongoing delirium on assessment by a psychiatry team and according to the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition. She was discharged on day 52 after her initial hospitalization to a long-term acute care facility.

Ms. A provided verbal consent for the case report but was unable to physically sign associated documentation because of infection-control measures.

## *Discussion*

### Pathophysiology

Neuropsychiatric presentations of COVID-19 are increasingly described in the literature. A retrospective case series of 214 hospitalized patients in China demonstrated that 24.8% had central nervous system (CNS) manifestations (e.g., dizziness, impaired consciousness, acute cerebrovascular disease, seizures), 8.9% had peripheral nervous system manifestations (taste, smell, and/or vision impairment), and 10.7% had skeletal muscular injury manifestations (10.7%).[6] Neurological abnormalities were observed in 45.5% of those severely ill with COVID-19 as compared to those less severely ill ($P = 0.02$), including impaired consciousness (14.8% versus 2.4%, $P < 0.001$).[6]

In general, delirium is present in up to 82% of ICU intubated patients.[7] Not surprisingly, ICU patients with COVID-19 and ARDS are similarly expected to have a high delirium incidence. Helms and colleagues[12] reported on 58 severely ill patients with COVID-19, with 69% agitated when weaning off sedation, and 65% of those were able to participate in the Confusion

Assessment Method for the ICU scoring positively, suggesting delirium.

The differential diagnosis of neuropsychiatric symptoms, including delirium, in patients with COVID-19 is extensive. Cases of encephalitis and meningitis have been documented with specific SARS-CoV-2 RNA detected in cerebral spinal fluid.[13] In addition, patients with COVID-19 might have elevated D-dimer and impaired platelet functioning, thus placing them at risk for acute cerebrovascular accidents.[14] Nonconvulsive seizures should also be entertained on the differential, based on the clinical picture.

Various pathophysiological mechanisms for delirium development and propagation have been proposed,[15] many of which coexist in patients with COVID-19. Some of these are unique to individual patients (i.e., substrates), some are related to the treatment environment (e.g., ICU, sedatives), and others are related to the acute effects of the virus and its comorbidities (i.e., precipitants). However, there are unique considerations in patients with COVID-19, including CNS viral effects, COVID-19–specific treatment side effects, and environmental factors.

Evidence suggests that direct CNS invasion of the SARS-CoV-2 is possible, which might lead to deleterious neuropsychiatric effects. In fact, animal studies have demonstrated that SARS-CoV-2 is neuroinvasive, likely entering the brain parenchyma via ascending olfactory nerves, then spreading to the thalamus and brainstem.[5]

In addition, a subset of patients with COVID-19 experience a cytokine storm.[16] While an immune response is important to fight the infection, an excessive and dysregulated immune overactivation is likely to contribute to the development of ARDS and multiorgan failure, including "brain failure" or delirium.[15] Many proinflammatory cytokines (e.g., interleukin-6, interleukin-8, interleukin-1 β) and chemokines (e.g., CCL2, CCL-5) have been linked to the development of ARDS, a frequent cause of mortality in patients with COVID-19[16]; the same have been associated with the development of delirium.[15] Specifically, Qin and colleagues[17] described extensive dysregulation of the immune response in patients with COVID-19. Moreover, cytokine storm is fueled by the release of catecholamines by immune cells via a self-amplifying circuit.[18] Catecholamines, such as norepinephrine, might also be elevated in hyperactive delirium, contributing to its pathophysiology and symptomology.[15] Ms. A's course was characterized by significant agitation, requiring the use of multiple high-dose sedatives. This agitation, along with ARDS, might be one presentation of the cytokine storm and catecholamine release in this patient population.

Among specific patient characteristics, older age among patients with COVID-19 is associated with higher morbidity and mortality rates.[19] Similarly, older age and associated medical comorbidities are recognized as major risk factors for delirium development.[15] In addition, patients with pneumonia and respiratory failure might experience CNS hypoxia and increasing anaerobic metabolism in the mitochondria of brain cells. This can then lead to cerebral vasodilation, brain cell and interstitial edema, and obstruction of cerebral blood flow.[14] These same mechanisms have been described as causative factors in delirium development.[15] Of note, Ms. A was an older woman.

Regarding treatment-related factors, patients with severe COVID-19 often require management in ICU settings and/or ventilatory support. Ventilated patients are frequently placed on combinations of CNS depressants to facilitate ventilatory compliance. Many of these sedatives are associated with an increased incidence of delirium.[15] In fact, owing to significant agitation in many patients with COVID-19 in the ICU and the risk to patients and staff associated with patients' dislodging lines and endotracheal tubes in context of high viral infectivity, patients have anecdotally required combinations of multiple sedatives with very high doses. In our case, Ms. A had required propofol, opiods, and high-dose benzodiazepines, among other agents, which could have all further worsened her confusion and agitation.

In addition, some medications that have been specifically used in the treatment of COVID-19 may themselves induce neuropsychiatric side effects. For example, hydroxychloroquine has been known to cause such side effects, including delirium.[20] These effects may be exacerbated by a cytokine storm–mediated increase in blood-brain permeability. While our patient was not treated with hydroxychloroquine, it might be an important consideration for others. Moreover, secondary complications, such as renal failure and secondary infections, can contribute to or worsen delirium.

Environmental factors also increase the risk of delirium during these challenging times. Owing to the high infectivity of this virus, shortage of personal

protective equipment, and medical isolation to decrease virus transmission, patients with COVID-19 might not have the benefit of conventional nonpharmacological prevention strategies or the support of loved ones.[21] The staff is unable to spend time and provide frequent reorientation and cognitive stimulation for the patients, while family members are not allowed to visit and provide visual cues, reassurance, and practical support. In addition, unusual configuration of the rooms, inability to recognize faces because of staff's extensive personal protective equipment, and potentially even the use of the virtual modalities to communicate (e.g., remote telemedicine and virtual visits with family members) as opposed to live visits all might worsen patients' perception of the reality and contribute to disorientation and confusion.

## Evaluation and Diagnosis

The diagnosis of delirium in patients with COVID-19 is challenging because of limited interactions between staff and patients due to isolation protocols. A live neuropsychiatric evaluation (gold standard) might not be available and/or safe; thus, screening tools, such as Confusion Assessment Method for the ICU[9] and the Intensive Care Delirium Screening Checklist,[22] might be especially useful. Yet, up to 30% of patients might not be able to complete screening tools that require patient participation.[9] Thus, a novel tool, the Stanford Proxy Test for Delirium, might be particularly helpful as it relies on nursing report of patients' cognition and behaviors, rather than on patient's participation.[10,11] Ms. A was initially evaluated remotely from outside of the room, integrating review of the chart and descriptions of her behavior and mental status from her nursing and medical staff. Confusion Assessment Method for the ICU and Stanford Proxy Test for Delirium were also used in her evaluation and diagnosis. As she improved and was able to engage in an evaluation, Ms. A was interviewed virtually with the use of telemedicine.

## Workup

In addition to usual infectious and metabolic workup for delirium, pharmacological agents that can contribute to mental status alterations must be reviewed. Our patient received significant amounts of deliriogenic medications (e.g., propofol, hydromorphone, oxycodone, chlordiazepoxide). Based on the differential diagnosis, brain imaging, a lumbar puncture, and an electroencephalogram might be indicated. As our patient did not display focal neurologic deficits, abnormal movements, or consistently depressed mental status, these studies were not indicated or pursued. Renal and liver function as well as QTc on electrocardiogram should be established to safely choose an appropriate pharmacological regimen. Ms. A had baseline elevated liver function tests (likely due to COVID-19 infection), and these were carefully monitored on a daily basis while VPA was administered on a short-term basis.

## Delirium Management

### *Nonpharmacological*

LaHue and colleagues[21] have suggested practical nonpharmacological interventions to prevent delirium in patients with COVID-19, given the unique challenges. Some practical nonpharmacological interventions in this population include maintaining light-dark environment consistent with the diurnal cycle; minimization of nighttime disruptions; reorientation and cognitive stimulation of the patient whenever possible; encouragement of family photos, phone calls, and virtual visits; provision of physical mobilization whenever possible; ensuring availability of glasses, hearing aids, and communication devices.

### *Medications and Monitoring*

Delirium-related agitation places the patient and health care providers at risk, thus medications should be available for acute management. While no studies have demonstrated pharmacological efficacy in the management of delirium among patients with COVID-19, we provide a framework for choosing psychotropic medications to assist in achieving behavioral control in ICU patients. Agents chosen to treat symptoms of delirium in our patient and included in Table 1 were specifically selected because of their own low deliriogenic potential and with the goal to minimize the use of conventional sedatives, which are associated with worsening delirium, longer recovery, and impaired long-term cognition.

At our center, the following medications have been used in management of agitation in patients with COVID-19 ICU-associated hyperactive delirium, including Ms. A, with the following considerations.

**TABLE 1. Pharmacological Options and Considerations in the Treatment of Hyperactive or Mixed COVID-19–Associated ICU Delirium**

| Medications | Mechanism of action | Rationale/indication | Dosing | Monitoring |
|---|---|---|---|---|
| Melatonin | - Melatonin receptor agonist<br>- Anti-inflammatory<br>- Antioxidant | - Regulates sleep-wake cycle and circadian rhythm<br>- Anti-inflammatory effect might be beneficial in COVID-19<br>- Recommended in all patients | 10–15 mg enteric at night (given around sundown) | - No specific monitoring required |
| Suvorexant | - Orexin antagonist | - Regulates sleep-wake cycle<br>- Helps in treatment of delirium, especially in combination with melatonin<br>- Recommended in all patients | 5–20 mg enteric at night | - Drowsiness |
| Alpha-2 agonists: dexmedetomidine, guanfacine | - Inhibit excess presynaptic norepinephrine release | - Downtitrate cytokine and moderate adrenergic storm<br>- Manage anxiety and agitation<br>- Consider dexmedetomidine for acute agitation and cycling<br>- Consider guanfacine to taper off sedative drips | Dexmedetomidine IV: 0.1–2.4 mcg/kg/h<br>Guanfacine enteric: 0.5 mg twice daily; 1 mg thrice daily | - Blood pressure<br>- Heart rate |
| Antipsychotics | - Dopamine antagonist | - Downregulate excess of dopamine inherent in delirium<br>- Recommended for distressing delirium symptoms and/or when patient poses threat to self and/or others | Haloperidol IV 0.5 mg–30 mg per 24 h | - QTc<br>Caution: COVID-19 associated with cardiac morbidity<br>Caution: some COVID-19–specific treatments may increase QTc<br>- Extrapyramidal side effects: rigidity |
| Anticonvulsants: VPA | - N-methyl-D-aspartic acid antagonist<br>- Anti-inlfammatory<br>- Blocks release of inflammatory cytokines (e.g., interleukin-6) | - Manages symptoms of hyperactive and mixed delirium (e.g., agitation, restlessness)<br>- May be administered IV or enterally<br>- Useful if cardiac or neurologic side effects of antipsychotics are a concern and/or when agitation persists despite an antipsychotic | 250–500 IV/enteric mg twice daily and titrate up to 500 mg in the morning, 500 mg in the afternoon, and 1000 mg at night | - LFTs<br>Caution: COVID-19 is associated with LFT elevations<br>- Platelets<br>- Ammonia levels<br>- VPA level (if concerned about toxicity or therapeutic level) |

COVID-19 = Coronavirus disease 2019; ICU = intensive care unit; IV = intravenous; LFT = liver function test; QTc = corrected QT interval; VPA = valproic acid.

High-dose melatonin is used for treatment of delirium and sleep-wake cycle regulation and postulated to be useful in the treatment of COVID-19 in general, given its anti-inflammatory and antioxidant effects.[23] We have maximized melatonin for Ms. A.

Suvorexant regulates sleep-wake cycle and assists in treatment of delirium, especially in combination with melatonin or melatonin receptor agonist.[24,25] Thus, it was added for management of sleep-wake cycle in this patient with hyperactive COVID-19–associated delirium.

Alpha-2 agonists decrease noradrenergic upregulation secondary to cytokine storm. While dexmedetomidine can be used for acute agitation and cycling at night, guanfacine can help taper off dexmedetomidine and other sedatives. Ms. A had already been managed with dexmedetomidine. Addition of guanfacine appears to have facilitated tapering off her other sedative drips, including dexmedetomidine.

Antipsychotics can assist in delirium symptom control, while patients must be monitored for QTc prolongation and neurologic and sedative side effects. Specifically in this patient population, antipsychotic agents must be carefully monitored, given the potential use of COVID-19–specific medications that may prolong QTc (e.g., hydroxychloroquine, azithromycin), leading to a potentially increased risk of torsades

de pointes,[26] as well as rare cardiac manifestations of COVID-19. QTc was monitored on a daily basis and was not prolonged for Ms. A. While increasing doses of quetiapine did not seem helpful for her, switching to haloperidol in combination with other interventions was correlated with improvement in Ms. A's mental status. Haloperidol might have been more helpful becaue of its more potent dopamine blockade and minimal antihistaminic and anticholinergic activity than quetiapine. In addition, haloperidol has been found to be an effective antagonist of sigma-1 receptors, which, in theory, might potently protect against oxidative stress–related cell death.[27] Nursing staff was educated on assessing for extrapyramidal side effects associated with antipsychotics, integrating this into their regular patient assessment and care.

VPA is used for management of hyperactive and/or mixed (i.e., fluctuating between agitation and hypoactivity) delirium, has potential anti-inflammatory and anti-oxidant effects, and might decrease transcription of interleukin-6.[28] Evidence also suggests potential neuroprotective effects of VPA.[28] VPA might assist to minimize or taper off sedative agents; however, liver function tests and platelets must be closely monitored. In this case, addition of VPA seemed crucial in decreasing agitation and assisting in tapering off multiple sedating drips as well as benzodiazepines and opiates.

## *Conclusions*

This case report discusses the proposed pathophysiology of COVID-19–associated ICU delirium. Derived from the clinical complexity of the patient described, we provide a framework to delirium evaluation and management in similar patients. As the number of cases of COVID-19 continues to increase, so will the hospital length of stay and inevitable incidence of delirium and agitation in these patients. Thus, a systematic approach to delirium prophylaxis, screening, diagnosis, and treatment are paramount to patients' management and improved outcomes.

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