Altered Mental Status in Patients Hospitalized with COVID-19: Perspectives from Neurologic and Psychiatric Consultants

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CASE HISTORY*

History of Present Illness

A 62-year-old man with a past medical history of asthma and opioid use disorder on methadone developed respiratory symptoms in mid-March, which progressed to subacute respiratory failure by early April. He was diagnosed with COVID-19 by nasopharyngeal RT-PCR and admitted to an academic New York City hospital. The patient was intubated for hypoxemia, sedated with propofol and fentanyl, and admitted to the medical intensive care unit (MICU). Laboratory testing revealed elevated serum levels of D-dimer at 1143 ng/mL (reference level <500 ng/mL), C-reactive protein at 73.70 mg/L (reference level <8 mg/L), and ferritin at 554 ng/mL, together reflecting a pattern of elevated inflammatory markers associated with severe COVID-19 infection. The patient's prolonged hospital course was complicated by numerous infections, including methicillin-resistant *Staphylococcus aureus* bacteremia (hospital day 8), vancomycin-resistant *Enterococus* bacteremia (hospital day 13), multidrug-resistant *Enterobacter* pneumonia (hospital day 14), and a *Pseudomonas*-positive urinary tract infection (hospital day 17), all of which were treated with multiple courses of antibiotics. Attempts to wean sedation and ventilatory support were complicated by the above infections and, when sedation was weaned, by ventilator dyssynchrony and agitation, resulting in the uptitration of propofol and maintenance on mechanical ventilation. Because of a need for prolonged respiratory support, the patient required tracheostomy on hospital day 10. By hospital day 14, the patient had developed acute kidney injury with creatinine elevated to 2.1 mg/dL, from a baseline 0.8 mg/dL at time of admission.

Neurology Consult, Medical Intensive Care Unit, and Hospital Floor

Sedation was gradually weaned over the course of nine days (beginning on day 26), and propofol and fentanyl infusions were stopped by hospital day 35. The patient remained unresponsive, however, and was not seen to react to attempts to examine him from the MICU team. On hospital day 39, our neurology service was consulted to evaluate for potential neurologic causes of his altered mental status, given his decreased arousal despite stopping sedation. Upon the neurology consultant's initial examination, the patient was comatose, breathing humidified air through his tracheostomy site with ventilator assistance, and not responding to verbal or even vigorous tactile stimuli. The patient exhibited no spontaneous movements of his extremities, either purposeful or adventitious. Although he occasionally grimaced to sustained noxious stimuli by nailbed pressure in each extremity, he exhibited no localizing responses and showed no evidence of purposeful withdrawal. No cranial neuropathies were evident, and brain stem reflexes remained intact—including the corneal, vestibulo-ocular, cough, and gag reflexes.

Given that the patient's neurologic exam was nonfocal but significant for globally diminished arousal, the consulting neurology team suspected that the patient's diminished level of consciousness was likely the result of an underlying toxic-metabolic encephalopathy. As background for this hypothesis, both initial media reports and first-hand experience by the neurology consult team (during the early phase of the pandemic reaching New York City) suggested acquired hypercoagulability and increased stroke burden as the predominant

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* **Patient privacy:** To protect the privacy of patients who came from vulnerable social backgrounds, lacked decision-making capacity, and were physically separated from family (visitors were not allowed in the hospital), this case history is a composite of multiple patients seen by the authors in New York City during the 2020–21 SARS-CoV-2 pandemic, and is representative of our experience. All aspects of the case history presented, including labs and quotations, were drawn from actual patients and were deidentified as much as possible to protect patient privacy while retaining clinically relevant information.

neurologic sequelae of COVID-19 illness. Thus, magnetic resonance imaging (MRI) of the brain was done to rule out neurovascular lesions or hypoxic-ischemic injury that may have been sustained via cerebral hypoperfusion from shock. MRI of the brain revealed no acute structural changes and only evidence of mild chronic microvascular disease affecting periventricular white matter.

Because neurology sought to rule out nonconvulsive status epilepticus as another plausible and common potential reason for the patient's diminished degree of arousal, continuous video-assisted electroencephalography (EEG) was done for a period of 36 hours. No seizures or epileptiform discharges were seen. The EEG revealed state-dependent diffuse waves with triphasic morphology superimposed on moderate diffuse background slowing and disorganization, which was most consistent with a severe toxic-metabolic encephalopathy. Neurology felt that the patient's diminished arousal reflected just such a toxic-metabolic encephalopathy, which could have resulted from a combination of prolonged cytokine-storming from a virally induced inflammatory state and all of the following: superimposed hospital-acquired bacterial infections; metabolic derangement; renal failure; and toxic effects of residual sedatives, antibiotics, and neuroactive drug metabolites.

Gradually, common offending agents for encephalopathy, including intravenous sedation, opioid pain medication, cephalosporins (including cefepime and ceftazidime), and antihistamines, were withdrawn. The patient remained hemodynamically stable for a prolonged period and was transferred to an MICU step-down unit that supported ventilated patients. On hospital day 46, neurology reexamined the patient and found him to be stuporous but no longer comatose. He responded to noxious stimuli by withdrawing the appropriate extremity. He briefly opened his eyes but did not respond verbally or show signs of being consciously attending to the examiner's presence. As the patient's fluid status improved and his kidney function gradually recovered, the patient's mental status improved such that he was thought to be capable of protecting his airway. His tracheostomy was reversed, and he was transferred to a medical floor and eventually to an acute rehabilitation facility.

Psychiatry Consult, Hospital Floor, and Rehabilitation Facility

The patient was transferred to an acute rehabilitation facility seven weeks after his admission to the hospital. While he gradually improved in his degree of alertness, the patient still required extensive prompting to participate in an interview or to make his needs known. In rehabilitation therapies, he was described as awake but restless and inattentive with little spontaneous speech output and markedly impaired behavioral initiation for anything other than self-directed tasks. With strong encouragement, he would attempt to participate in simple therapy tasks but would quickly become irritable, expressing his frustration by abruptly shouting profanities or attempting to push therapy materials, or the therapists themselves, away. His sleep patterns were dysregulated, with the patient tending to nap during the day between therapies and wake at night, at which time he would bang repeatedly on his bedrails and attempt to climb out of bed despite being too weak to ambulate on his own. He required constant observation to ensure his safety. He resisted nursing attempts to administer necessary nebulizer treatments and intermittently refused oral medications. Therapists reported that he was making no progress. Psychiatry was ultimately consulted to assist with behavior management and to facilitate participation in rehabilitation.

On initial psychiatric evaluation he was observed to be affectively flat, showed signs of psychomotor slowing, and made repeated attempts to eat soup with a fork throughout the interview. He was inattentive and on one occasion began picking at an invisible item on his tray. He said his name when asked but otherwise he answered most questions, "I don't know" or simply looked away. Speech was monotonous, with prolonged latency, and there was no spontaneous speech. He was alexithymic with regard to his mood and did not describe his mood when prompted or showed signs of indifference. After a few minutes into the interview, he became restless and began banging on his wheelchair, concluding the encounter.

Psychiatry diagnosed mixed hypoactive and hyperactive delirium. Low-dose valproic acid was added to reduce impulsivity during the day. To reduce circadian rhythm dysregulation, it was recommended that he be moved to a bed with a window and that, in between therapies, he be seated in his wheelchair in the hallway by the nursing station in order to provide social stimulation and prevent napping. Melatonin 6 mg at 8 p.m. was added to facilitate nighttime sleep. Within a week, he was sleeping through the night. His daytime alertness improved, and restlessness and agitation decreased, but he continued to present as flat, apathetic, and minimally engaged in treatment. Catatonia and akinetic mutism were considered. Given the possibility of catatonia, antipsychotics were avoided during this period lest their administration worsen the patient's condition or otherwise confound the diagnostic process via polypharmacy. Despite the absence of limb rigidity or posturing to support the diagnosis of catatonia, it was felt that his significant weakness could mask these motor features. Lorazepam challenge was nevertheless deferred, given concerns about sedation, and amantadine was added for its potential benefit in both akinetic mutism and catatonia.

Titration of amantadine to 200 mg twice a day over ten days produced marked improvement in speech output and behavioral initiation. He was calm, attentive, and increasingly communicative, and able to participate in longer rehabilitation therapy sessions and interviews. He complained of diffuse body pain. He became more affectively expressive, presenting as dysphoric and tearful at times, describing depressed mood and hopelessness. He stated that he wished he had died of COVID-19 and that he would rather be dead than unable to walk on his own. He described frightening intrusive memories of being "suffocated in a storage closet," "paralyzed and blinded by constant lights," "with bodies everywhere" —which were often triggered by nursing attempts to administer nebulizer

treatments. These memories were interpreted as flashbacks to his experience in an overloaded, makeshift ICU. Psychiatry reexamined the patient and recommended initiation of duloxetine, which was uptitrated to 60 mg daily over the course of the following month. The patient's cognitive status improved, with him able to state he was in a hospital (though he was unable to name the specific rehabilitation center) and to identify the year correctly, though not the month. His attention improved, and he was able to recite the months of the year backward correctly through August before giving up. While the patient continued to voice passive suicidal ideation, this lessened as he began to engage more with physical therapy and made gains in stamina and confidence.[†]

QUESTIONS TO THE CONSULTANTS

- To Ariane Lewis, MD (neurocritical care): As a neurointensivist, how has your role been redefined or changed during the COVID-19 pandemic? What do you think about this patient's altered mental status, and how would you go about ruling out focal neurologic causes that might be responsible for it? What patterns have you observed in evaluating patients with COVID-19 who had altered mental status?

- To Adrienne D. Taylor, MD (consultation-liaison psychiatry): As a consultation-liaison psychiatrist, how has your role been redefined or changed during the COVID-19 pandemic? What patterns have you observed in COVID-19 patients who experience altered mental status or delirium? What are some of the specific challenges that you have experienced in managing agitation in this population?

- To Lindsey Gurin, MD (psychiatry and neurology): As a dual-boarded psychiatrist and neurologist who has consulted on COVID-19 patients across a range of clinical acuity, what patterns have you observed in terms of patients' neuropsychiatric presentations, and how do you conceptualize these presentations in terms of brain-behavior relationships? How has your role differed, depending on whether you were consulted as a psychiatrist or a neurologist?

Ariane Lewis, MD

By 8 April 2020, 990 critically ill patients with COVID-19 were already hospitalized at the four hospitals affiliated with my medical center in New York.[1] Because my colleagues in the Division of Neurocritical Care were redeployed to COVID-19 ICUs, I saw all neurocritical care consults at our hospital between 30 March and 1 May. Neurocritical care consults for the majority of patients with COVID-19 during this period were due to altered mental status that the primary team felt was more profound or more protracted than that which they would typically expect for a critically ill patient. The degree of altered mental status varied, and while some patients were delirious (with reduced attention, awareness, and memory, and orientation that fluctuated), others were obtunded (with mild to moderate reduction in alertness and slowed psychological responses to stimulation), stuporous (responsive only to continuous vigorous stimulation), or comatose (unarousable to any form of stimulation).[2] There were myriad toxic-metabolic reasons for every patient to develop altered mental status, including any of the following: prolonged treatment with high doses of sedation; sepsis due to both COVID-19 itself and hospital-acquired infections such as pneumonia, bacteremia, and urinary tract infections; hypoxia; and acute renal failure.[3] However, declaring that encephalopathy in a critically ill patient with COVID-19 is toxic-metabolic requires careful consideration of other potential etiologies for altered mental status,[4] as was done in this case.

First and foremost, it is necessary to determine if a patient with altered mental status has any focal findings. The patient described here had a nonfocal examination. Nonetheless, when an examination reveals globally diminished arousal, as was seen in this case, it is necessary to have an extremely low threshold to obtain imaging in critically ill patients with COVID-19 who are stable to be transported out of the ICU. Focal findings due to stroke can be masked in this patient population due to quadriparesis caused by critical illness neuropathy or myopathy. Patients with COVID-19 are hypercoagulable and have elevated D-dimers, which often prompted empiric initiation of anticoagulation at our institution,[5] with the consequence that these patients are at risk for both ischemic and hemorrhagic strokes.[5–7] In a few cases, a request to evaluate a patient for altered mental status led to the discovery of a devastating bleed.[5]

Aside from ruling out stroke, imaging is also beneficial in patients with COVID-19 who have altered mental status because some patients develop white matter changes with or without microhemorrhages.[8] In the case described here, both stroke and white matter changes were ruled out based on the MRI, which showed only mild chronic microvascular disease. Follow-up imaging was not obtained, but if it had been, it likely would have shown similar chronic changes.

Although this patient did not show any clinical evidence of seizure activity, workup of his encephalopathy included an EEG to rule out nonconvulsive status epilepticus. Cytokine storming, systemic and central nervous system infection, electrolyte abnormalities, and renal failure can cause nonconvulsive seizures, which lead to change in mental status.[9,10] Because of the pandemic, my institution, like other hospitals, reduced performance of EEGs to limit the risk of viral transmission.[11] However, because data prior to the pandemic has shown that approximately 15% of critically ill patients have nonconvulsive seizures, EEGs were still performed for some patients to rule out nonconvulsive seizures when all other workup was unrevealing.[12] The patient described here had evidence of triphasic waves on his EEG, which are the result of toxic-metabolic derangements. Absence of epileptiform findings on his EEG is unsurprising, given that he did not have a

[†] The case history was prepared by Daniel Talmasov, MD, Sean M. Kelly, MD, PhD, and Lindsey Gurin, MD.

history of seizures or any clinical events suggestive of seizures; epileptologists at my hospital retrospectively found that the presence of epileptiform findings on an EEG in this patient population was associated only with a history of epilepsy or the presence of clinical seizures.[13]

Notably, this patient did not have cerebrospinal fluid (CSF) testing to work up his encephalopathy, as this is not done routinely on all patients with COVID-19. It is worth mentioning, however, that there have been reports of encephalitis due to COVID-19.[14–16] None of the patients who had CSF testing at my hospital had a positive SARS-CoV-2 PCR in the CSF.[17] It remains unclear whether the reports of positive SARS-CoV-2 PCR in the CSF represent true viral invasion into the central nervous system, versus contamination, and if these are true positives, by what mechanism the virus enters the central nervous system.

The degree and time course of neurologic recovery in critically ill patients with COVID-19 are highly variable. While some patients I consulted on ultimately improved neurologically, others remained in a vegetative state throughout the duration of their admissions until they were discharged to a long-term care facility or the goals of care were transitioned to a focus on comfort. I frequently discussed the uncertainties of neuroprognostication in this patient population with critical care teams and families. Further research is needed to explore the neurologic outcome for patients with COVID-19 who, like the one described here, have encephalopathy. Fortunately, this patient survived his acute hospitalization and was able to be discharged to acute rehab. He subsequently experienced psychiatric complications, however, which will be discussed by my colleagues.

Adrienne D. Taylor, MD

As the days of the pandemic progressed, we saw rapid changes to our psychiatric consultation service, including challenging new clinical scenarios of patients with multiple medical comorbidities and new or unfamiliar medications. We needed to familiarize ourselves with the medications' mechanisms of action, their neuropsychiatric side effects, and their possible interactions with psychotropics.[18] Various units across the hospital were quickly transitioned to ICU beds to handle the growing need. When responding to consults in the COVID-19 ICUs, we saw increasing levels of distress in our physician and nursing colleagues, as they became consumed by the intricacies involved in the care of their critically ill patients, by exposure to more patients and more deaths, and by the uncertain outcomes of treatment.

We noticed a need for more collaboration in treating delirium and encephalopathy. Our expertise not only was vital for providing relief from the burden of agitation management but also allowed for us to provide targeted peer support—to help process fear, frustration, exhaustion, and grief. These challenges led to an expanded implementation of our proactive model of consultation, which had been previously used in the teaching medical ICU,[19] led by our consultation-liaison fellows with attending supervision. Our increased presence with primary teams also allowed us to provide a more in-depth evaluation of potential causes or contributions to delirium, highlight the importance of ongoing treatment of underlying psychiatric disorders, and provide education to medical and nursing staff on the management of behavioral disturbances in the ICU patients.

A key change in our role has been that consultation-liaison psychiatrists are increasingly being asked to help manage the neuropsychiatric sequelae in COVID-19 patients. In general, delirium is present at high rates (up to 82%) of ICU intubated patients,[20] with similar incidence in patients with COVID-19 and acute respiratory distress syndrome. COVID-19 has been shown to be associated with encephalopathy, prominent agitation, and corticospinal tract signs.[21] In some cases, patients can present with confusion and agitation in the absence of respiratory symptoms or other signs of infection.[22] Case reports have also described catatonia-like syndromes and akinetic mutism, considered to be low dopamine states, with exams notable for varying degrees of myoclonus, immobility, withdrawal, rigidity, alogia, and abulia.[22]

The current hypotheses regarding the etiology of severe delirium caused by COVID-19 include the direct viral effect in the central nervous system, stroke, cytokine release syndrome, polypharmacy, and hypoxia, along with typical risk factors associated with delirium such as neuronal aging, social isolation, circadian disruption, and renal and hepatic injury.[23,24] Inflammatory cytokines and chemokines, including IL-6 (which has been thought to correlate with disease severity), have been found to be significantly elevated and may account for increased incidence of delirium in COVID-19 patients.[25]

Our service primarily received requests to assist ICU teams with the management of severe agitation as patients recovered from respiratory failure, as described in the case here. During the stabilization of these critically ill patients, ICU teams have needed to use increasingly higher doses of medications, including propofol, fentanyl, midazolam, dexmedetomidine, and phenobarbital, for sedation, ventilation, and the control of dangerous behaviors. The maintenance and weaning phases of mechanical ventilation have been found to be prolonged by two weeks or more in COVID-19 patients, which contributes to the extended use of sedating medications and also opioids and benzodiazepines.

Our psychiatrists found that patients often benefited from a slower taper of sedating medications. Use of low-dose antipsychotics or transition from dexmedetomidine to clonidine[26,27] earlier in the course often allowed for the faster taper of sedatives and a smoother weaning period. At the height of the pandemic, we found the need to create new algorithms for managing agitation in these patients, given the supply shortages of medications used for sedation, including lorazepam, dexmedetomidine, and propofol, and limited options because of the level of organ dysfunction. Higher doses of psychotropic medications for managing behavioral dysregulation or perceptual disturbances were common—and required close attention, with frequent vital signs and continuous cardiac,

pulse oximetry, and capnometry monitoring. Preexisting opioid agonist therapy (methadone in the case of the patient presented here) should also be continued to limit contributions of opioid withdrawal to delirium, with short-acting supplemental analgesia administered as needed for acute pain.[28]

Antipsychotics remain the gold standard for managing agitation in delirium. Particularly, clinicians may consider use of low-potency antipsychotics, given the lower risk of extrapyramidal side effects and the increased rates of parkinsonism and catatonia in COVID-19 patients.[29] It is also important to recognize the risk of prolonged QTc, given the various therapeutics that have been used in the course of treating COVID-19, including chloroquine, hydroxychloroquine, and azithromycin. This risk can be problematic in patients with tenuous cardiac status; frequent electrocardiogram monitoring or telemetry is necessary.[18] Dopamine agonists or benzodiazepines should also be considered for patients presenting with catatonia or akinetic mutism, as in the case described here, despite the potential to worsen delirium.[29]

Valproic acid (VPA) is commonly used for managing agitation, impulsivity, and dysexecutive syndromes in the setting of delirium in critically ill patients.[30–32] VPA may also be especially useful in COVID-19 patients, given the lack of effect on QTc and the increased risk of strokes, seizures, and abnormal electroencephalogram findings in these patients.[29] VPA is thought to exert its actions through effects on dopamine, glutamate, norepinephrine, and serotonin, and may decrease CNS oxidative stress and neurotoxicity.[30] Our consultation service often used VPA as a standing agent to decrease the "basal" level of agitation and also as an acute agent for episodes of behavioral dysregulation. It is important to remember that VPA may have a longer onset of action, depending on the route given to the patient, when compared to antipsychotics. In cases of severe and difficult-to-control agitation, VPA may also be used with standing or as needed low-dose antipsychotics to provide better coverage of these psychiatric and behavioral disturbances. In COVID-19 patients on VPA, trough serum levels, ammonia levels, and liver function tests, including lipase, should be checked 48 hours after initiation. Monitoring for pancreatitis and liver dysfunction may be particularly important. Liver injury is commonly seen in COVID-19, with possible etiologies that include viral infection, drug-induced liver injury, and systemic inflammation due to cytokine storm or hypoxia.[26,33,34] Providers should consider supplementing with levocarnitine when hyperammonemia occurs.[34] If mental status worsens and hyperammonemia continues, VPA should be discontinued.

The higher doses and extended intubation periods also translated to increased frequency in the use of physical restraints. Adverse events associated with prolonged use of restraints and sedatives, including apnea and respiratory depression, can be substantially more dangerous in patients with COVID-19 in light of the rapid deterioration in the clinical course, profound hypoxia associated with active infection, and discordance between clinical and imaging evidence for the degree of pulmonary involvement.[35] Moreover, the ability to implement noncoercive and reorientation strategies in treating agitation and delirium was limited by social distancing and isolation measures to minimize the spread of COVID-19.[36] Clinicians quickly found that they had to make difficult decisions that took into account the substantial risk that agitated delirium presented for the health care worker (due to the likelihood of self-extubation and aerosolization of the virus) and that weighed it against the clinical and ethical consequences of using physical restraints, which could result in physical and psychological harm to the patient. We frequently emphasized the importance of treating underlying psychiatric illness and encouraged primary teams not to underestimate the risk of agitation. We counseled teams that the threshold for using pharmacotherapy and restraints is often lower, given the elevated risk of infection to both patients and the staff—and potentially became even lower when our health care system experienced shortages of the personal protective equipment needed for reintubation, engagement, and care of patients with COVID-19.

As patients do start to recover, many of them will continue to experience altered cognition with long-standing perceptual disturbances resulting in anergia, apathy, and compromised sleep upon discharge.[21,22] In the setting of underlying COVID-19 infection, recovering delirium, social isolation, and a prolonged and complicated hospital stay, the risk of developing symptoms consistent with depression, anxiety, insomnia, and trauma- and stressor-related disorders is also increased.[37,38] Notably, the patient in the case described here experienced depression, suicidality, and trauma-related symptoms requiring intervention and initiation of an antidepressant. It can be difficult to ascertain whether the emergence of psychiatric symptoms, particularly depression and anxiety, are a representation of new psychopathology after a delirium episode or, instead, the recurrence and continuation of a preexisting psychiatric illness. Psychiatric distress may also be a result of the pharmacologic and behavioral management of anxiety and agitated delirium. It is important to screen for signs of psychiatric distress throughout the course of treatment and recovery.

In the coming months, we will continue to learn, adapt, collaborate, and provide support to our colleagues and hospital system. Consultation-liaison psychiatrists should recognize that our role within the system puts us in an excellent position to advocate for both our patients and our colleagues' mental health and well-being, allowing us to work on a larger scale with community and hospital administration as we continue through the next phases of the pandemic.

Lindsey Gurin, MD

Consciousness, defined as the state of awareness of the self and environment, comprises two primary components: level, driven by brain stem–ascending arousal pathways; and contents, mediated by cortical networks.[2] Disruption of either or both of these systems may produce a wide range of presentations of altered mentation, from deep coma to agitated delirium,

all of which are subsumed under the umbrella terms of *altered mental status* or *encephalopathy*. Nowhere is the breadth and depth of the spectrum of global brain dysfunction—and the importance of collaborative effort between neurologists and psychiatrists—more on display than in patients hospitalized with COVID-19.

In practice, it is often the level of arousal and psychomotor features associated with encephalopathy in a given case that dictate whether neurology or psychiatry will be consulted initially. Patients with decreased arousal and limited purposeful behavior typically prompt neurology consultation. At the extreme low end of this spectrum are the disorders of consciousness (DoC), further characterized as coma; the vegetative state/unresponsive wakefulness state (VS/UWS), in which arousal is preserved but behavioral evidence of environmental awareness is absent; and the minimally conscious state (MCS), in which behavioral evidence of consciousness is definite but inconsistent.[39] A diagnosis of MCS confers a relatively better prognosis than VS/UWS,[40] but misdiagnosis may occur in up to 40% of patients.[41]

Since evaluation of consciousness necessarily depends upon a patient's ability to demonstrate behavioral evidence of various cognitive capacities, clinical assessment of DoC can be confounded by fluctuating arousal or by linguistic or motor impairments impeding comprehension or execution of commands. In patients with COVID-19, the differential diagnosis for decreased behavioral responsiveness must include motor weakness, as can be seen in the following contexts: prolonged neuromuscular blockade, critical illness neuropathy and myopathy, and Guillain-Barré syndrome; severe parkinsonism; and disorders of initiation and volition such as akinetic mutism and catatonia. A possible association is emerging between COVID-19 and parkinsonism, with cases reported of worsening motor features in Parkinson's disease patients who contracted COVID-19[42] and also of new-onset parkinsonian and akinetic-rigid syndromes occurring in encephalopathic patients with COVID-19 who did not have premorbid movement disorders.[22,43–45] In addition, catatonia has been described in patients with COVID-19 with[46,47] and without[48] premorbid psychiatric histories. Distinguishing DoC from severe parkinsonism, akinetic mutism, and catatonia requires careful assessment. If parkinsonism or akinetic mutism is suspected, dopaminergic therapies may be of benefit; if catatonia, benzodiazepines; and in all three instances, amantadine, a glutamate N-methyl-D-aspartate receptor antagonist that secondarily modulates dopamine, may be effective, as was the case here.[22]

Where prolonged DoC is confirmed, attempts should be made to characterize the syndrome as VS/UWS versus MCS in order to inform treatment and prognostication, keeping in mind that the degree to which the natural history of DoC due to COVID-19 may parallel that of DoC due to other nontraumatic etiologies of severe brain injury is not yet known. In one case, a patient with prolonged unresponsiveness due to COVID-19 and with MRI evidence of structural injury to bilateral subcortical and limbic structures nevertheless demonstrated intact default mode network connectivity on resting-state functional MRI and subsequently recovered consciousness after a two-month delay, highlighting the importance of avoiding early therapeutic nihilism in these patients.[49] Amantadine improves outcomes in patients with prolonged traumatic DoC,[50] and zolpidem, a selective agonist at the γ-aminobutyric acid–A receptor, may restore consciousness in a small percentage of patients with DoC of all etiologies.[50] The utility of these agents in patients with DoC due to COVID-19 is not known. At our center, amantadine and modafinil, a wakefulness-promoting agent originally approved for the treatment of excessive daytime sleepiness associated with narcolepsy, were most commonly used for patients with prolonged unresponsiveness due to COVID-19, with mixed results.

My colleagues have described the proposed mechanisms by which COVID-19 and SARS-CoV-2 may contribute to encephalopathy. It is likely that some combination of these mechanisms disrupts the frontal-subcortical circuitry subserving consciousness and volitional movement to produce the depressed arousal and diminished purposeful behavior seen in some patients with COVID-19. Hypoxic-ischemic injury to the brain stem and basal ganglia structures certainly plays a role in many cases[17] and figures prominently in post mortem neuropathological assessments of COVID-19 patients,[51] though some patients manifest abulia or akinetic mutism without having had known hypoxic respiratory failure.[22] Bilateral globus pallidus injury, known to be associated with post-hypoxic akinetic disorders[52] and apathy,[53] has been described in case reports of patients with COVID-19[54,55] and was frequently present in my anecdotal experience evaluating patients with severe encephalopathy due to COVID-19.

It has been suggested, based on animal studies, that severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERSCoV)—which are related—have a neurotropism with a preference for the brain stem and thalamus, but this hypothesis remains speculative.[56–58] Similarly, reports of post-COVID parkinsonism have led to renewed interest in a single decades-old study suggesting an association between Parkinson's disease and the presence of CSF coronavirus antibodies.[59] Case reports have suggested the possibility of inflammatory and hemorrhagic lesions in the brain stem, basal ganglia, thalamus, and medial temporal lobes,[60–62] but small post mortem neuroimaging[63] and autopsy[51] studies of deceased patients with COVID-19 have not presently demonstrated brain stem involvement. Whether or not SARS-CoV-2 may directly target the brain stem, basal ganglia, or dopaminergic neurons in some patients remains to be explored definitively.

At the other end of the COVID-19 encephalopathy spectrum are the patients with confusional states whose hyperarousal and behavioral agitation are likely to trigger psychiatric consultation. Here, too, disruption of frontal-subcortical and limbic circuitry may play a role. The pyramidal neurons in the cornu

ammonis–1 (CA1) region of the hippocampus and in layers 3, 5, and 6 of the neocortex are exquisitely sensitive to hypoxia,[64] setting the stage for disorders of memory, attention, and executive function that may predispose patients with COVID-19 to delirium once consciousness is recovered. In light of the possibility of direct viral invasion of the brain stem, one wonders if disinhibition of brain stem arousal pathways by virally mediated or inflammatory disruption of thalamo-limbic circuits could be producing early agitation and dysautonomia in these patients, as is hypothesized to be the case in agrypnia excitata,[65] with ultimate progression to central respiratory failure and persistent DoC in some patients.

During the first wave of the pandemic, I saw patients with COVID-19 encephalopathy as a neurologist, on a general neurology consult service; as a psychiatrist, on a general psychiatry consult service; and as a neuropsychiatrist consulting to an acute inpatient rehabilitation unit that had been repurposed for COVID-19 recovery. On the neurology team, we were asked to see profoundly encephalopathic or comatose patients, whereas on the psychiatry team we were more often consulted for assistance with the behavioral disturbances occurring as patients entered into, or emerged from, hypoxic respiratory failure. In the acute rehabilitation setting, we saw a wide range of evolving cognitive impairments, mood symptoms, and early trauma- and stressor-related disorders. Demoralization in the context of severe weakness and burning neuropathic pain was common. A number of patients told me their last clear memory was of agreeing to be intubated; regaining consciousness sometimes more than a month later, they described feeling blindsided by the severity of their impairments.

Ultimately, as is nearly always the case in the care of patients with neurobehavioral disorders, comprehensive consultation occurs simultaneously at two levels: that of the individual patient, offering guidance in the clinical evaluation and management of the issues in question; and that of the patient-team dyad, addressing the unspoken questions, frustrations, and uncertainties that arise during the care of medically ill patients presenting with aberrant behavior. This crucial "liaison" role explicitly informs consultation-liaison psychiatry, but it is also highly relevant to neurologists, and it was unexpectedly on the general neurology service that I found myself most embodying the role of a consultation-liaison psychiatrist.

The vast majority of neurology consult requests were for patients with persistent severe impairments of consciousness; while these were framed as requests for guidance in diagnosis and management, the etiology and catastrophic extent of brain injury were self-evident in most cases. Feeling initially helpless, frustrated, and demoralized by these consults, our team considered the psychodynamics of providing ICU care to neurologically devastated COVID-19 patients and began to understand the subtext of these requests to be a desire for moral support in the face of an unprecedented combination of illness acuity, treatment futility, and sheer clinical volume. We shifted our approach to incorporate liaison elements borrowed from psychiatry and spoke openly with teams not just about what we could do for their patients, but about what we could do for them. We reviewed charts, confirmed neurological exams, and discussed the complexity and uncertainty of neuroprognostication with teams and families in detail to assist in end-of-life decision making.[66] As these teams made efforts to *be with* severely ill patients and their families, and to provide emotional presence and guidance even when no further medical interventions were possible, we sought to do the same for them.

The COVID-19 pandemic offers an opportunity to examine the ways in which neurologists and psychiatrists can contribute, collaborate, and be differentially utilized in the care of patients with various presentations of encephalopathy. Moving forward, clinicians familiar with the short- and long-term neurobiological and psychological impact of COVID-19—on patients and on those caring for them—will be essential as we confront subsequent waves of the disease.

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