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Complexities of Delirium in COVID-19: A Case Series

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ABSTRACT

Since the onset of the COVID-19 pandemic in December 2019, the world is rapidly learning about the variable presentations of the novel coronavirus (SARS-CoV-2). While the initial focus was on respiratory symptoms and sequelae of the virus, there are now a growing number of reports that are describing neuropsychiatric complications of SARS-CoV-2, including delirium. The management, treatment, and complications of delirium are very well documented in the literature, however the COVID-19 pandemic has presented us with new difficulties in dealing with an old syndrome. In this case series, we seek to describe the unique challenges we encounter with delirious patients in the context of SARS-COV-2 infection.

INTRODUCTION

We are living in a momentous time; our world has been gripped by the virulent, enigmatic, and potentially lethal novel coronavirus (SARS-CoV-2). SARS-CoV-2 infection (COVID-19) can have variable presentations ranging from asymptomatic infection to fatal severe acute respiratory syndrome (SARS) [1]. Multiple neurological complications of advanced COVID-19 illness have been described, including cerebrovascular accidents, encephalopathy (delirium), encephalitis and new-onset psychosis [2,3]. As consultation-liaison psychiatrists, we are navigating these unprecedented times and striving to practice good medicine despite a dearth of concrete knowledge and understanding regarding this pathogen. The COVID-19 pandemic has created novel challenges in dealing with one of our oldest syndromes, delirium. Elderly patients in the hospital are known to be more susceptible to delirium due to their increased age, multiple medical comorbidities, susceptibility to infections, polypharmacy, and presence of chronic cognitive deficits [4,5]. COVID-19 patients are especially at increased risk for developing delirium due to several factors including their age, hypoxia, use of sedatives during mechanical ventilation, immobility, neuro inflammatory and vascular factors [6,7]. To date, there are few reports describing the unique complications and challenges in delirious patients who are also infected with SARS-CoV-2. In this report, we present two patients hospitalized with complications of COVID-19 who developed delirium. These cases highlight the differential diagnostic and management challenges we have faced in treating delirium in COVID-19 patients during this evolving pandemic.

CASE 1

Mr. F was a 79 y/o man with a history of bipolar disorder and a medical history of hyperlipidemia. His psychiatric history was significant for longstanding mood

disorder symptoms- including manic spells characterized by compulsive overspending, and several severe depressive episodes, several psychiatric hospitalizations, and a history of electroconvulsive therapy. For the last 10 years he was stable, maintained on valproic acid and bupropion. He lived with his wife in a private apartment, and continued to work in a small business, riding public transportation in New York City. He had no apparent memory dysfunction.

His daughter brought him to our hospital, an academic tertiary referral center 20 miles north of New York City, in early March of 2020. The family was concerned about the patient's recent change in mood, described as a two-week history of mood swings, irritability, decreased appetite, and fatigue. He was initially seen in the psychiatric emergency room, where he presented as well nourished and kempt appearing, conversant and appropriate; he discussed stressors including the recent death of his brother, and loneliness due to social isolation. He reported compliance with his psychotropic medications. He was diagnosed with Adjustment Disorder with Depressed Mood, and he was released from the medical emergency room with a recommendation to follow up with his outpatient psychiatrist.

Mr. F's family brought him back to the emergency room two days later, reporting that he'd been refusing to eat, and had a fever of 101F at home. On examination he was afebrile but weak and lethargic; his white blood cell count was normal at 6.8 k/mm3 (ref 4.8-10.8 k/mm3), a chest X-ray was clear, urinalysis was unremarkable, blood alcohol level was undetectable, urine toxicology negative, and blood chemistries revealed normal electrolytes, transaminases, a blood urea nitrogen of 27 mg/dL (ref 6-22 mg/dL), and a creatinine of 1.28mg/dL (ref 0.72-1.25 mg/dL). Inflammatory markers were not checked upon admission. He was admitted to the internal medicine service of the hospital for altered mental status, and acute kidney injury due to dehydration. His oxygen saturation on room air was 92% and he was maintained on oxygen via nasal cannula, 2-3 liters per minute. Psychiatry was re-consulted for a concern that the patient's altered mental status was due to a clinical depressive episode. At that time the patient was found to be confused - he was moaning and writhing in bed and had disrobed. He was unable to say the date, month, year, or location, and additionally performed poorly on bedside tests of attention. He was unable to report his medical history. He did not endorse depressed mood.

A diagnosis of major depressive episode was considered, but the presentation was one of acute confusion and not one of depressed mood and lack of enjoyment of usually pleasurable activities [8]. A diagnosis of dementia was also considered due to his forgetfulness. The history from collateral informants was not consistent with dementia, given that he had been independently functioning prior to the acute onset of this episode. Based on this presentation, he was diagnosed with delirium, with hypoactive features [9].

On hospital day 3, he was refusing to take food or liquids by mouth, and was found to have erythematous throat with exudate; otolaryngology consultation diagnosed viral upper respiratory tract infection on hospital day 3. Blood and throat cultures were negative at that time, and the patient continued to have a normal leukocyte count. On hospital day 4, the patient had low grade fevers, and ceftriaxone and metronidazole were initiated. A CT scan of the neck was obtained to rule out peritonsillar abscess. CT neck showed no evidence of peritonsillar abscess, however there were moderately severe airspace opacities in the upper lungs with a peripheral predominance. This finding raised concern for a lower respiratory infection, and CT scan of the chest again demonstrated this finding and demonstrated mediastinal lymphadenopathy. Respiratory multiplex panel, blood, and urine cultures were negative. Procalcitonin level was in the normal range . The patient was tested for COVID-19 with a nasopharyngeal swab, and the test was negative. He was found to have high epstein-barr virus PCR (EBV DNA 12,818, (ref <500 cp/mL)), concerning for lymphoproliferative disorder or other malignancy. He became volume overloaded and had pleural effusions and was diuresed with intravenous furosemide; trans-thoracic echo demonstrated a normal ejection fraction of 60%. He was treated empirically for candida esophagitis. CT Scan of the abdomen and pelvis showed no abdominal or pelvic lymphadenopathy. He was planned for a bronchoscopy to further workup these diagnostic possibilities; however the test was delayed due to need for repeat COVID testing prior to an aerosol generating procedure. Inflammatory markers were found to be elevated on hospital

day 8: C-reactive protein was 20.0mg/dL (ref 0.00-0.50 mg/dL) and ferritin 1038.1 ug/L (ref 18.0-37.0 ug/L).

In subsequent days his mental status waxed and waned; at times he appeared lucid, conversant, and appropriately concerned about his physical status; at other times he appeared withdrawn and disoriented. The patient had ongoing alterations in mental status; he was mostly disoriented and lethargic but had occasional motor restlessness. He refused to take oral food, fluid, or medications. The psychiatric consultant did not recommend specific treatment for the delirium because the behavioral manifestations were not treatment-interfering. Given the lack of focal neurological findings, neuroimaging was not felt to be indicated.

On hospital day 12 the patient developed diarrhea, increased white blood cell count (12.6 k/mm3 (ref 4.8-10.8 k/mm3)), and respiratory distress, with an oxygen saturation of 88% on 3 liters per minute via nasal cannula. He required venti-mask but was maintaining oxygen saturation in the 90's. On hospital day 13 his oxygen saturation dropped to 75% and he was put on 100% oxygen without improvement. He was intubated and given furosemide. A close family member tested positive for SARS-CoV-2 that day. The Patient's tracheal aspirate was obtained and he was positive for COVID-19 via the real-time PCR assay. The Patient had a 2-week course in the intensive care unit, where he was intubated and comatose; sadly, Mr. F. expired 1 month after his initial presentation to our hospital.

CASE 2

Mr. S is a 69 year old male with no prior psychiatric history, and a past medical history of coronary artery disease, hypertension, hyperlipidemia, former smoker, who initially presented to a community hospital in early April 2020 with a one-month history of exertional dyspnea and cough. While he was initially diagnosed with congestive heart failure, his admission chest X-ray showed patchy infiltrates and upon testing, he was positive for SARS-CoV-2. He was started on hydroxychloroquine, azithromycin and diuretics, and he was discharged home after a few days.

At home he continued to have shortness of breath and lower extremity edema, and returned to the community hospital three weeks later for further evaluation of these symptoms. Echocardiogram revealed an ejection fraction of 20%, and he was sent to our tertiary referral center for cardiac catheterization which showed occlusion of several arteries. Upon admission, the patient was afebrile, intermittently hypotensive, with a normal respiratory rate, and an oxygen saturation ranging from 91-96%. His labs showed an elevated platelet count (459 k/mm3, range: 160-410 k/mm3), BUN (33 mg/dL, ref range: 6-22 mg/dL), lactate dehydrogenase (258 U/L, ref range: 125- 220 U/L), CRP (11.0 mg/dL, ref range: 0.00-0.50 mg/dL), ferritin (330.1 ug/L, ref range: 18.0- 370 ug/L), D-Dimer (10.60 mg/L, ref range: < 0.59 mg/L_FEU) and fibrinogen (631 mg/dL, ref range: 180 - 400). PT and PTT were mildly elevated at 12.4 sec (ref range: 9.8- 12.0 sec) and 32.5 sec (25.0- 32.0 sec), respectively. He again tested positive for SARS-CoV-2. The cardiothoracic team decided he would need coronary artery bypass grafting, however the patient continued to be positive for SARS-CoV-2, with his chest Computed Tomography (CT) scan showing ground glass opacities in both lungs. Given the severity of his cardiac disease, the cardiothoracic team decided to do the procedure immediately.

Post-operatively, he remained intubated, was on Extracorporeal Membrane Oxygenation (ECMO), and was placed on fentanyl, propofol and dexmedetomidine drips. He was extubated on postoperative day 3. Psychiatry was consulted on postoperative day 5 for hallucinations. At the time of the initial psychiatric evaluation, the patient was oriented to person, place, time, and situation and was able to follow simple commands; however, he had difficulty with attention tasks. The nursing staff reported that the patient's mental status was waxing and waning, and that he was experiencing visual hallucinations and periods of disorientation. The differential diagnosis for new-onset psychosis includes primary psychiatric etiologies, such as schizophrenia, or a major affective episode with psychotic features; or a psychosis secondary to a general medical condition. In this case, the patient was well beyond the typical presenting age for a new-onset schizophrenia, and additionally he did not have any accompanying features of a new-onset schizophrenia. He had no history of an affective disorder, and he had no current symptoms consistent with a depressive or manic episode. Given the fact that Mr. S had a significant cognitive impairment, a primary neurocognitive disorder was also considered; however, his cognition at baseline was normal, and the changes to his

memory and attention occurred during his postoperative course. He was not receiving any medications known to cause delirium. Neuroimaging showed areas of chronic infarct, but no acute cerebrovascular accident. His oxygen saturation and kidney, liver, and metabolic functioning were normal except for an elevated lactate dehydrogenase (436 U/L, ref range: 125-220 U/L).

He was diagnosed with a delirium, likely due to the aftereffects of anesthesia and acute illness. He was not started on any psychotropic medications because he was not agitated. Over the next 48 hours, he developed pulmonary emboli and adrenal insufficiency and was started on hydrocortisone. Thereafter, the patient developed hyperactive features of delirium and started to pull at his therapeutic lines and monitoring devices. He persistently tried to get out of bed, necessitating frequent redirection by his nurses and patient care technicians, who were stationed outside of his room due to the airborne isolation precautions that COVID-19 patients require. In an effort to minimize staff interaction, the staff could not implement strategies to help with orientation, sleep-wake cycle regulation, noise reduction and mobility. Additionally, visitor restrictions and the need to wear Personal Protective Equipment (PPE) did not allow for a sense of comfort and familiarity for the patient.

To assist with behavioral management of this patient, the consulting psychiatrist recommended oral valproic acid 250mg twice daily, and oral quetiapine 25 mg every eight hours as needed. Intravenous haldol was considered but not started because the patient was also on a QTc- prolonging agent, amiodarone, and also because of his recent cardiac surgery. He remained agitated, and the dose of valproic acid was increased to 250 mg in the morning, and 500 mg in the evening. He received the quetiapine intermittently.

While the valproic acid reduced his agitation, he was too restless and impulsive to be safely managed without a one to one nursing sitter. Because of the SARS-CoV-2 airborne isolation precautions, the assigned sitter was unable to sit in the room with him, and was only able to watch him outside of his room through the glass panels. Unfortunately, due to visitor restrictions his family was unable to visit, and because we were trying to minimize staff interaction, Mr. S was unable to video call with his family. Mr. S eventually was transferred to the floors where he tested negative for SARS-CoV-2 and his delirium eventually resolved.

DISCUSSION

Delirium and neurophysiology

Delirium is an acute or subacute encephalopathy [8], characterized by an acute change in mental status with altered levels of awareness and inattention. Other symptoms of delirium include disorientation, memory loss, language disturbances, and perceptual disturbances such as hallucinations (See Box 1). Delirium represents a change from the patient's baseline, and the symptoms often have a variable presentation over time, known as waxing and waning [9]. Delirium is common in patients with serious illness, with an incidence of approximately 20% in hospitalized patients [10]. Delirium can be caused by a range of underlying conditions, including toxic, metabolic, infectious, and structural perturbations. Management of delirium involves first identifying and addressing the underlying factors contributing to the delirium. Behavioral management for delirium is very important, and involves regulation of sleep-wake cycle, reorientation by staff, assuring adequate stimulation with assistive hearing and visual aid devices, having family and familiar caregivers at bedside, and providing an appropriate level of social stimulation, early mobilization, appropriate assessment and treatment of pain [4]. In the United States, there are no FDA-approved medication treatments for delirium; antipsychotic drugs such as haloperidol, risperidone, and quetiapine are frequently employed to manage psychotic symptoms and agitation accompanying delirium. Second-line pharmacologic treatments for delirium include anti-epileptic drugs such as valproic acid, carbamazepine, and gabapentin; alpha-2 agonists such as dexmedetomidine, and NMDA-receptor blocking agents (amantadine, memantine) [4].

Both cases exhibited characteristics of delirium. Full-blown delirium is generally divided into subtypes, including hypoactive, hyperactive and mixed [4]. In Case 1, the main symptoms were inattention and altered levels of consciousness; this would have been classified as a hypoactive delirium. In Case 2, there was a preponderance of hallucinations and this patient also experienced psychomotor agitation and behavioral disturbances, classifying this as a hyperactive delirium. While the patients in both of these cases shared a

common underlying infection, the manifestation of their deliria existed along the continuum. While the delirium in Case 1 was clearly related to the patient's COVID positive status, the delirium in Case 2 was likely more multifactorial. In Case 2, the patient's initial COVID presentation may have triggered his heart failure and subsequent cardiac complications, leading to multiple factors contributing to his delirium presentation.

Box 1 Diagnostic criteria for delirium

From The Diagnostic and Statistical Manual of Mental Disorders, 5th edition

- A disturbance in attention (i.e., reduced ability to direct, focus, sustain, and shift attention) and awareness (reduced orientation to the environment).
- The disturbance develops over a short period of time (usually hours to a few days), represents a change from baseline attention and awareness, and tends to fluctuate in severity during the course of a day.
- An additional disturbance in cognition (e.g., memory deficit, disorientation, language, visuospatial ability, or perception).
- The above disturbances are not better explained by another preexisting, established, or evolving neurocognitive disorder and do not occur in the context of a severely reduced level of arousal
- There is evidence that the disturbance is the direct physiological result of another medical condition, substance intoxication or withdawal, or toxin exposure, or due to multiple etiologies.

Neurologic features have been reported in great numbers of COVID-19 patients. In one series of consecutive admissions to a hospital for ARDS due to COVID-19, 65% of patients screened positive for delirium. Agitation was present in 69% in that study [11]. In a retrospective case series of deceased COVID-19 patients, 20% of patients had encephalopathy [12]. Another study shows that neurologic manifestations tend to occur early in the illness (median time, 1-2 days) [13]. Beach et al. described four cases in which the patients presented with delirium, and lacked other core features of COVID-19 [14]. The authors postulate several mechanisms for delirium. The infection can cause a secondary encephalopathy due to inflammatory effects of the virus: breakdown in endothelium, blood-brain barrier, and can cause a cytokine storm [14]. There have been reports of encephalitis, and also it is postulated that SARS-COV-2 can invade the brain via the olfactory bulb [14]. Most likely is a hybrid model, in which both direct and indirect factors contribute to the development of delirium in COVID-19 patients [14].

Delirium as a presenting symptom

These cases highlight several aspects of delirium in the context of COVID infection. First, delirium can be the initial presenting symptom in COVID-19 patients. In Case 1 altered mental status was the presenting complaint; delirium was diagnosed based on this patient's acute onset and fluctuating course. Initially the patient experienced few respiratory symptoms and had an intermittent fever; therefore, there was not a high index of suspicion for a respiratory illness. CT imaging incidentally showed lower respiratory illness, which persisted and was widespread. Various etiologies for the lower respiratory inflammation and lymphadenopathy were considered, and it cannot be known whether he had COVID-19 from the time of admission, or whether he contracted it during his hospital course. The US Centers for Disease Control and Prevention does not list 'altered mental status', 'confusion' or 'delirium' as a symptom to "watch for" [15]. Thus, patients presenting with altered mental status/delirium as the initial symptom may be overlooked as being infected with SARS-CoV-2. Delayed diagnosis due to an atypical presentation can lead to increased dissemination and disease burden of the virus.

Diagnostic uncertainty

In Case 1, there was diagnostic uncertainty. The patient had a chronic psychiatric condition and recent psychosocial stressors; while his presentation was one of altered mental status, there was a question as to whether the mental status changes could be attributed to a clinical depressive episode of bipolar disorder. Additionally, basic workup was negative for infection; and while the patient was eventually diagnosed with COVID-19, he initially had a negative test. Careful assessment of the mental status in Case 1 by an experienced psychiatrist revealed the cardinal symptoms of delirium - altered level of consciousness, inattention and a waxing/waning presentation. Because of this assessment the patient was kept on the medicine service rather than being transferred to the psychiatry service, and workup eventually revealed the SARS-COV-2 infection. In Case 1, the patient did not require specific pharmacologic management of delirium, primarily because of the hypoactive presentation.

Management of delirium in COVID positive patients

In Case 2, the behavioral manifestations of the delirium in the context of SARS-CoV-2 infection represented a significant management challenge. While his delirium may have been more related to undergoing major cardiac surgery, his COVID positive status made treating his delirium difficult. Delirium is managed through non-pharmacological interventions consisting of frequent re-orientation, sleep enhancement protocols, early mobility, and correction of hearing or visual impairments [16,17,18]. Several of these methods had to be modified or could not be implemented due to the patient's positive status

[6]. The patient required one-to-one nursing observation, however hospital isolation protocol dictated that he would be watched from outside of his room rather than inside. This diminished the opportunity for this patient to receive an appropriate level of cognitive stimulation and to be frequently reoriented [7]. Other behavioral management strategies for delirium include having loved ones and familiar caregivers at bedside [4,16,17]; these measures were also unavailable to this patient because of the visitor restrictions in place during the COVID-19 peak in New York in April and May of 2020. Additionally, the patient placed hospital staff at increased risk for transmission of SARS-CoV-2 by pulling at PPE and his lines, and requiring nurses to frequently enter his room. Therefore, there was a reliance on psychopharmacologic management for the behavioral disturbances in Case 2. This case highlights additional management challenges, including the risk of using antipsychotics in a patient with a complex cardiac history and with other QTc prolonging agents.

These challenges call for modified guidelines for treating delirium in patients with COVID-19 during this unprecedented time. Substituting strategies that require staff interaction, with methods that the patient can do independently, can help manage the patient's delirium while minimizing further dissemination of the virus. Using crossword puzzles and word finds can help cognitively stimulate the patient [19]. Teaching patients' range of motion (ROM) exercises that they can complete unassisted can replace in- person physical therapy [19]. Access to tablets and smartphones can help patients communicate with families and retain some familiarity in an unfamiliar environment [20]. The use of net beds in severely agitated patients may reduce the need for restraints and thus reduce the risk of rhabdomyolysis and thrombosis [20]. Figure 1 summarizes the management of delirium and presents modified treatment strategies to assist in the care of patients with COVID-19 [18,20].

CONCLUSION

Although these cases highlight different presentations and time courses of delirium, they raise similar differential diagnostic and treatment concerns about delirium in the context of COVID-19. In terms of differential diagnosis, there are many confounding factors that can cloud the clinical picture, such as the presence of prior psychiatric illness, the concurrent stress of the COVID-19 pandemic, and the variable presentation of delirium. It is therefore important to bear in mind the diagnostic criteria for delirium, and do a careful mental status examination to rule in or out the cardinal features of delirium. Further, it is important to note that a delirium or other neuropsychiatric presentation may be the first presenting symptom of underlying COVID-19 infection. Environmental treatment interventions for delirium, such as frequent reorientation, reassurance, and social stimulation have been difficult to provide while hospitals have engaged in increased use of PPE and limited visitation to prevent the spread of COVID-19.

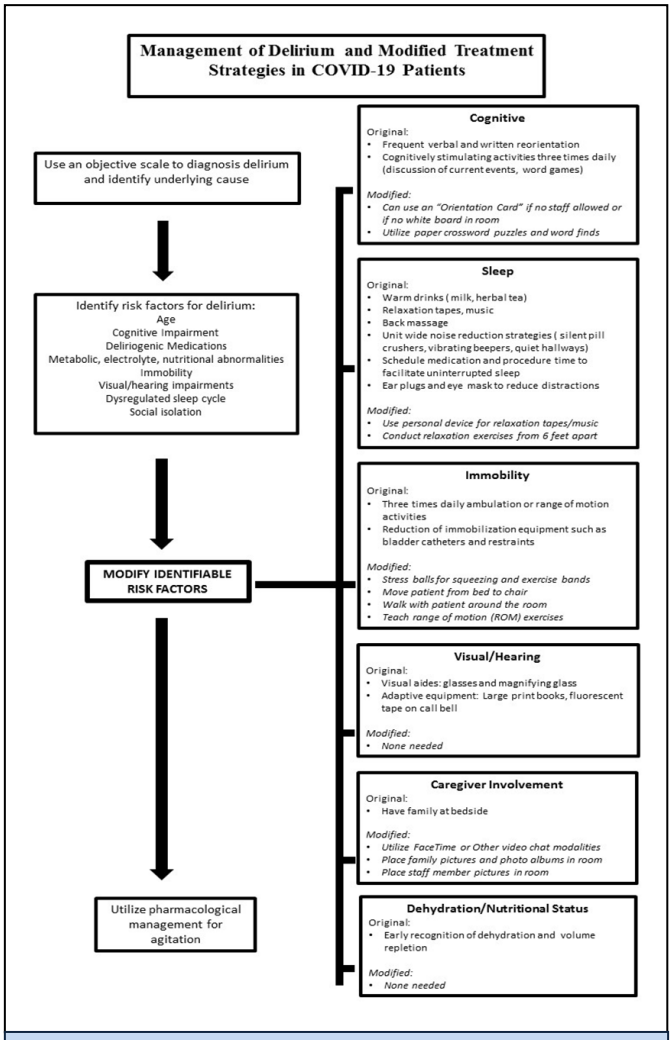

Figure 1: Management of Delirium and Modified Treatment Strategies in COVID-19 Patients.

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