Unprovoked serotonin syndrome-like presentation of SARS-CoV-2 infection: A small case series

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Abstract
Clinicians and researchers have reported an array of neurological abnormalities in coronavirus disease 2019 (COVID-19), and while serotonin excess has been observed we are unaware of reports of central nervous system serotonin toxicity in COVID-19. We present two cases that resemble serotonin syndrome in COVID-19, but without identifiable inciting medications. A 54-year-old with multiple sclerosis and diabetes mellitus presented with altered mental status. His altered sensorium was attributed to diabetic ketoacidosis, but his condition quickly deteriorated with fever to 105 degrees Fahrenheit, rigidity in all extremities, inducible clonus, and hyperreflexia. He was intubated and was treated for possible meningitis and seizure. Neurologic workup was negative for acute pathology. Despite acetaminophen, his core temperature remained elevated to 105 degrees Fahrenheit. He was treated with external cooling and cyproheptadine and within 48 h, his fever, rigidity, hyperreflexia, and clonus resolved. He was extubated and discharged home on day 14. A 72-year-old with hyperlipidemia was admitted with tremors, 4 days after testing positive for COVID-19. His symptoms rapidly worsened, and he was transferred to the Intensive Care Unit on day 3 in extremis, febrile to 104.4 degrees Fahrenheit, heart rate of 180 beats per minute, and apparent whole body myoclonus. He was intubated and developed fever refractory to acetaminophen requiring external cooling. Extensive neurologic workup was negative. He received cyproheptadine and slowly improved. He was extubated and discharged to rehab on day 11. These cases represent a unique presentation in COVID-19 that must be considered and requires a high index of suspicion.

Keywords
Central nervous system, coronavirus, cyproheptadine, serotonin, serotonin syndrome

Background
While a majority of the focus in coronavirus disease 2019 (COVID-19) has been on the common and often fatal lung disease, reports of neurologic dysfunction have been increasing since the pandemic began.¹ ² The spectrum of neurologic disease has been broad, from encephalopathy to thromboembolic disease,¹ ² among a series of other pathologic mechanisms described by others.³ ¹² While these reports have not described serotonin syndrome-like manifestations per se, the evidence is mounting in regard to the presence of elevated plasma serotonin levels in COVID-19 patients,¹³,¹⁴ both in severe and non-severe disease, thought to be a result of an intense degree of platelet activation and serotonin liberation from activated platelets due to severe acute respiratory distress syndrome 2 (SARS-CoV-2) infection.¹³,¹⁵,¹⁶ Clinically, ¹Critical Care Medicine, Lexington Medical Center, West Columbia, SC, USA ²Internal Medicine, Lexington Medical Center, West Columbia, SC, USA ³Neurology, Lexington Medical Center, West Columbia, SC, USA ⁴Critical Care Clinical Pharmacy, Novant Health Forsyth Medical Center, Winston-Salem, NC, USA ⁵Division of Gastroenterology, Saddleback Medical Group, Laguna Hills, CA, USA ⁶Division of Trauma and Surgical Critical Care, Louisiana State University Health Sciences Center Shreveport, Shreveport, LA, USA ⁷Participating Study Center, Lexington Medical Center, West Columbia, SC, USA  

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Serotonin toxicity is an increasingly recognized condition that carries a significant risk of morbidity and mortality if left undiagnosed and untreated. Studies prior to COVID-19 showed that a sizable portion of delirium encountered in the Intensive Care Unit (ICU) could be attributed to unrecognized serotonin toxicity, with culprits including fentanyl, among other medications. Given these lines of biochemical and clinical evidence, it is possible that unrecognized serotonin toxicity may be more frequently present in COVID-19 and may contribute significantly to morbidity and mortality.

The diagnosis of serotonin toxicity is one of exclusion and requires a thorough history, identification of offending medication(s), and fulfillment of established diagnostic criteria (Table 1). We recently encountered two critically ill COVID-19 patients who met the clinical criteria for serotonin syndrome, but neither had identifiable provoking serotonergic medication use. Both patients had extensive evaluations and both clinically improved with supportive care and additional treatment that included serotonin receptor (5HT-2A) antagonism with cyproheptadine.

### Case presentations

We present two cases of COVID-19 manifesting serotonin syndrome-like illness successfully treated with cyproheptadine. The case series received exemption from the Lexington Medical Center Institutional Review Board.

#### Patient 1

A 54-year-old male with the past medical history of diabetes mellitus type 1 (DM1), hypertension (HTN), and multiple sclerosis (MS) presented to the emergency department (ED) with altered mental status and hypoxemia. The family reported several days of diarrhea preceding his presentation and brought him in due to altered mental status. In the ED, he was hypoxemic, responding to low flow oxygen. His labs were notable for hyperpyrexia and a temperature of 105 degrees Fahrenheit. His core temperature rapidly rose to 105 degrees Fahrenheit and was refractory to acetaminophen. A lumbar puncture showed no evidence of infection. He required intubation and mechanical ventilation to protect his airway with concern for possible seizures induced by severe hyperpyrexia.

Despite external cooling, he remained febrile and progressed to a persistent state of extreme muscle rigidity diffusely, most pronounced in the lower extremities, along with hyperreflexia and inducible clonus. An electroencephalogram (EEG) showed severe, diffuse slowing with no seizure activity.

He met the Hunter Serotonin Toxicity Criteria and the Sternbach Criteria and was therefore started on cyproheptadine orally to manage serotonin toxicity. A thorough medication review, with the assistance of the patient’s pharmacy and his wife, including documentation of all over-the-counter medication and supplement use, failed to reveal any recent or new potentially offending serotonergic medications.

His fever quickly resolved with cyproheptadine initiation. Given his MS history, magnetic resonance imaging (MRI) of the brain and spine were obtained and revealed a stable appearance of multifocal demyelinating plaques with no new lesions identified. He remained on the ventilator with continuous propofol infusion and scheduled cyproheptadine for.

#### Table 1. Serotonin syndrome diagnostic criteria.

| Criteria                          | Hunter Criteria                      | Sternbach Criteria                      |
|-----------------------------------|---------------------------------------|-----------------------------------------|
| Mental status changes             | Spontaneous clonus                    | \( \geq 3 \) of the following + serotonergic use: |
| Hyperreflexia                     | Ocular clonus + agitation or diaphoresis| \( \geq 1 \) of the following + serotonergic use: |
| Shivering                         | Tremor + hyperreflexia                |                                        |
| Diarrhea                          | Hypertonic and temperature >38 degrees Celsius + ocular clonus or inducible clonus |
| Fever                             |                                        |                                        |
| (Sensitivity 75%, specificity 96%)| (Sensitivity 84%, specificity 97%)     |                                        |
96 h. He was successfully extubated to 1 L nasal cannula 4 days after intubation, with resolution of encephalopathy and no clinically apparent return of the acute neuromuscular signs. He was maintained on scheduled cyproheptadine and continued to improve during his inpatient stay. He was transferred out of the ICU 1 day after extubation and discharged home with home health on hospital day 14.

Patient 2

A 72-year-old male with a past medical history of hyperlipidemia and gastroesophageal reflux disease (GERD) presented to the ED with severe tremors, which started 3 days prior and had progressively worsened. He had developed fever 2 days earlier and was found to be diagnosed with COVID-19 with positive for SARS-CoV-2 PCR. Evaluation in the ED included a CT scan of the head, which was negative for acute pathology. He was given intravenous lorazepam in the ED with no improvement and admitted to the general medical floor for further evaluation. Neurology consultants attributed his abnormal motor changes to multifocal myoclonus. He was started on intravenous lorazepam. MRI of the brain revealed no significant pathology, and EEG performed during the abnormal movements was interpreted as normal. His clinical status quickly deteriorated and he was transferred to the ICU on day 2 of admission with violent, whole body tremors, sinus tachycardia to a heart rate of 180 beats per minute, altered mental status, and hyperpyrexia to 104.4 degrees Fahrenheit. Neurologic exam was difficult due to the violent tremors, but he did demonstrate severe rigidity and inducible clonus, similar to patient 1. His clinical status remained unchanged despite boluses of intravenous lorazepam, leading to intubation for airway protection. He was pan-cultured and treated empirically with broad-spectrum antibiotics. Like patient 1, he also met the Hunter and Sternbach Criteria, and consequently, treatment with cyproheptadine was initiated. A similarly comprehensive medication review with his pharmacy and his family, including documentation of all over-the-counter medications and supplements, failed to reveal potentially offending serotonergic drugs. As per standard therapy, he was started on corticosteroids for the treatment of COVID-19. With these interventions his fever resolved within 24 h. He remained on continuous propofol infusion with scheduled cyproheptadine. Similar to patient 1, his neurologic abnormalities abated with the maintenance of sedation but returned, to a lesser degree, with sedation holidays, although his mental status had improved. An EEG was repeated on day 3 of intubation and revealed general slowing of the background rhythm. On day 4 of mechanical ventilation, he was extubated to room air with only mild intention tremor and some truncal ataxia. His weakness and ataxia quickly resolved with inpatient physical therapy, and his tremor nearly resolved before discharge to a rehabilitation facility on hospital day 11.

Discussion

Both of our patients had a constellation of concerning findings including inducible clonus, hyperreflexia, tremor, hyperpyrexia, and encephalopathy. Both fulfilled the diagnostic criteria for serotonin toxicity, except that neither patient had an identifiable provoking serotonergic agent. Such clinical presentations, in the context of the recently published biochemical evidence of elevated plasma serotonin in patients with COVID-19 raise the possibility of serotonin toxicity being an inherent result of SARS-CoV-2 infection itself. Two of the most extensive series to date describing the neurologic findings in COVID-19 found that more than 60% of patients with severe COVID-19 exhibited diffuse corticospinal tract signs, including hyperreflexia and myoclonus, lending more credence to the possibility that serotonin toxicity is perhaps present more than previously thought in COVID-19, and raising the question of whether such recognition and treatment may improve patient outcomes in COVID-19.

Serotonin toxicity may present in a highly variable fashion, and its signs and symptoms can overlap tremendously with sepsis and acute respiratory distress syndrome (ARDS), thus remaining challenging to recognize. Signs more specific for serotonin toxicity include neuromuscular hyperactivity (myoclonus and hyperreflexia), neurologic findings less frequently observed in sepsis and ARDS of other etiologies. The diagnosis of serotonin toxicity is typically one of exclusion. All accepted diagnostic criteria require an offending serotonergic medication to fulfill and establish the diagnosis; this contrasts with the two cases reported here, where no offending serotonergic drugs were identified. Our patients initially deteriorated clinically despite standard COVID-19 therapy. Both responded favorably and relatively rapidly (relative to the typically long course of COVID-19 critical illness) to cyproheptadine initiation, exhibiting a rapid reversal of the clinical signs of serotonin toxicity, as well as with favorable overall outcomes with the maintenance of cyproheptadine.

That both cases described here required a longer course of cyproheptadine than that described with classic serotonin syndrome is worth discussing further. While serotonin syndrome usually resolves within 24 h of removal of the offending agent and therefore may require a much more brief course of cyproheptadine, the provocateur of elevated plasma serotonin in COVID-19 is thought to be an immune-driven state of platelet activation. Recent evidence supports the presence of such platelet-activating autoantibodies in sera of COVID-19 patients. Such platelet-activating autoimmunity formed acutely in response to SARS-CoV-2 infection may plausibly last at least a few days and possibly longer (akin to heparin-induced thrombocytopenia) in the most severe cases of COVID-19, and therefore result in persistent platelet activation and serotonin release from platelets into plasma during this timeframe. Consequently, antiserotonergic therapy with
cyproheptadine may be required for a more extended period in the most severe cases of COVID-19, and recurrence of serotonin toxicity may be evident with premature cessation of cyproheptadine.

Conclusion
These case reports raise the possibility that serotonin toxicity may develop spontaneously in patients with COVID-19. Clinicians caring for COVID-19 patients must maintain a high index of suspicion for this reversible entity, even in the absence of identifiable offending serotonergic medications. Serotonin toxicity is reversible with cyproheptadine administration and avoidance of exacerbating serotonergic medication use. While continuing to search for other etiologies, empiric treatment with cyproheptadine may offer a low risk, potentially high reward therapy in this very ill patient population.

Author contributions
P.K. and M.S.-J. collected clinical data from the EMR. All authors equally contributed to the writing of the manuscript. All authors read and approved the final manuscript.

Availability of data and materials
Data sharing is not applicable to this article as no data sets were generated or analyzed during this study.

Declaration of conflicting interests
The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Ethical approval
The planning, conduct, and reporting of this publication are in accordance with the Helsinki Declaration, as revised in 2013. Our institution does not require ethical approval for reporting individual cases or case series. We received a waiver from the Institutional Review Board (IRB) at the Lexington Medical Center.

Funding
The author(s) received no financial support for the research, authorship, and/or publication of this article.

Informed consent
Written informed consent was obtained from the patient(s) for their anonymized information to be published in this article.

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