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Delirium in COVID-19: A case series and exploration of potential mechanisms for central nervous system involvement

Scott R. Beach*, Nathan C. Praschan, Charlotte Hogan, Samuel Dotson, Flannery Merideth, Nicholas Kontos, Gregory L. Fricchione, Felicia A. Smith

Department of Psychiatry, Massachusetts General Hospital and Harvard Medical School, Boston, MA, United States of America

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ABSTRACT

Introduction: Neuropsychiatric manifestations of the coronavirus disease 2019 (COVID-19) have been described, including anosmia, ageusia, headache, paresthesia, encephalitis and encephalopathy. Little is known about the mechanisms by which the virus causes central nervous system (CNS) symptoms, and therefore little guidance is available regarding potential workup or management options.

Cases: We present a series of four consecutive cases, seen by our psychiatry consultation service over a one-week period, each of which manifested delirium as a result of infection with severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2).

Discussion: The four cases highlighted here all occurred in older patients with premorbid evidence of cognitive decline. Unique features seen in multiple cases included rigidity, alogia, abulia, and elevated inflammatory markers. In all four cases, a change in mental status was the presenting symptom, and three of the four cases lacked significant respiratory symptoms. In addition to discussing unique features of the cases, we discuss possible pathophysiologic explanations for COVID-19 delirium.

Conclusions: Delirium should be recognized as a potential feature of infection with SARS-CoV-2 and may be the only presenting symptom. Based on the high rates of delirium demonstrated in prior studies, hospitals should consider adding mental status changes to the list of testing criteria. Further research is needed to determine if delirium in COVID-19 represents a primary encephalopathy heralding invasion of the CNS by the virus, or a secondary encephalopathy related to systemic inflammatory response or other factors.

1. Introduction

Initial descriptions of the manifestations of the coronavirus disease 2019 (COVID-19) have focused on respiratory and occasionally gastrointestinal symptoms. These symptoms, in addition to constitutional symptoms such as fever and chills, are also the symptoms most screened for in hospitals and clinics when deciding whether individuals warrant testing for the disease. While the typical symptom cluster for the sickest patients is acute respiratory distress syndrome (ARDS), atypical presentations are increasingly being recognized.

Attention is starting to be paid to the emergence of neuropsychiatric presentations of the disorder, including acute encephalopathy. It is estimated that more than one-third of patients with COVID-19 develop neuropsychiatric symptoms, including headache, paresthesia, and disturbed consciousness, and neuropsychiatric symptoms seem to be associated with more severe disease [1]. In a recent case series of 58 patients, 49 (84%) developed neuropsychiatric symptoms, including 40 (69%) with agitation, 26 (65%) with positive findings on the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU) scale, and 14 (36%) with dysexecutive syndrome [2]. It is also known that up to 88% of patients develop anosmia or ageusia, thought to be secondary to invasion of the olfactory bulb by the virus, suggesting brain involvement [3]. Coagulopathies leading to acute cerebrovascular disease are a known complication of ARDS-related disseminated intravascular coagulation (DIC). Guillain-Barre syndrome has been described as a complication [4], and a case report has also highlighted an acute hemorrhagic necrotizing encephalopathy (AHNE) resulting from infection with COVID-19, thought to be possibly related to cytokine storm [5]. In addition to these specific pathologies, a case series from Wuhan demonstrated that at least 20% of patients who eventually died from COVID-19 had evidence of encephalopathy [6]. While the preceding accompaniments of the virus may be interpreted as indirect CNS effects, a report from China describes the first case of viral encephalitis with COVID-19, confirmed by cerebrospinal fluid (CSF) analysis [7].

* Corresponding author at: Department of Psychiatry, Massachusetts General Hospital, 55 Fruit Street/Warren 605, United States of America.
E-mail address: sbeach1@partners.org (S.R. Beach).

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Despite these reports, and consistent with their etiological ambiguity, little is known about the spectrum of COVID-19's central nervous system (CNS) presentations, the potential for CNS symptoms in the absence of other manifestations, the pathophysiology underlying these presentations, and approaches to their treatment. While it is perhaps not surprising that delirium is common in patients with COVID-19, given the severity of illness and the fact that those suffering from complications of the illness are frequently older and have underlying vulnerabilities, some specific features of the delirium and hypotheses about the ability of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) to penetrate the CNS raise the question of whether a secondary delirium might not fully explain the phenomenon.

In this case series, we describe the first four consecutive patients with delirium in the setting of known acute infection with SARS-CoV-2 seen on the psychiatry consultation service of a large general hospital over a one-week period. All patients were positive for SARS-CoV-2 on polymerase chain reaction (PCR) testing conducted via nasopharyngeal swabs on the cobas 6800 system, which detects two SARS-CoV-2 RNA targets. We discuss overlapping and unique features among these cases. We also hypothesize potential explanations for the observed features of COVID-19 delirium. To our knowledge, this is the first case series in the United States to characterize delirium in COVID-19.

2. Cases

2.1. Case 1

Mr. A is a 76-year-old former male boxer, living in an assisted living facility (ALF) with a history of major neurocognitive disorder with behavioral disturbance and psychotic features and alcohol use disorder in sustained remission for 30 years. He had one prior psychiatric hospitalization one month prior to this presentation, for agitation and psychosis. Medical history includes coronary artery disease (CAD) s/p percutaneous coronary intervention (PCI) in 1997, atrial fibrillation, congestive heart failure (CHF), and hypertension. He was admitted to the medical floor after presenting with paranoia and new aggression toward staff at his ALF. Non-contrast head computed tomography (NCHCT) was unremarkable beyond age-related small vessel disease and mild generalized volume loss. At presentation, he was febrile to 100.8 ˚F, with borderline leukopenia (white blood cell count [WBC] of 4.0 k) and a chest X-ray (CXR) showing bibasilar opacities. His C-reactive protein (CRP) was elevated on admission to 50.7 mg/L (reference range < 8 mg/L). Respiratory status was stable. SARS-CoV-2 PCR test, prompted by CXR, was positive. Per hospital protocol he was treated with atorvastatin, azithromycin and hydroxychloroquine for 5 days. His only home psychiatric medication was olanzapine 2.5 mg at night, which was initially continued on admission. Psychiatry consultation was obtained on hospital day (HD) #1. On examination by the psychiatry consultant, prior to obtaining any new antipsychotic medication and despite normal tone at baseline prior to admission, he was noted to have multifocal myoclonus in his bilateral upper and lower extremities, cogwheeling in bilateral upper extremities, increased tone in bilateral lower extremities without ankle clonus, and a positive grasp and palmomental reflex. Lumbar puncture (LP), electroencephalogram (EEG) and magnetic resonance imaging (MRI) of the brain were not obtained. He displayed restlessness and purposeless striking out, requiring soft restraints for much of his hospitalization. His respiratory and hemodynamic status remained stable. Over the first three days of hospitalization, he had minimal speech production progressing to near mutism, despite normal verbal output at baseline. Starting on HD #4, oral and intramuscular (IM) olanzapine (2.5–10 mg) and later intravenous (IV) haloperidol (4 mg daily) were used to manage agitation, with limited success but without development of extrapyramidal symptoms (EPS) or other adverse side-effects. A unilateral livedoid rash of the right lower extremity was noted during the second week of hospitalization. His CRP peaked on HD #8 at 148.8 mg/L. On HD #12, IV chlorpromazine was initiated at a dose of 25 mg twice daily and titrated to 25 mg daily and 50 mg nightly with resolution of agitation and restlessness. By HD #18 he was started on a clonidine patch at 0.1 mg daily with a plan to titrate off IV chlorpromazine after his family decided to transition him to comfort measures only in consultation with palliative care on HD #19. He was noted to be more alert and conversant beginning on HD #19, though intermittent behavioral dysregulation continued.

2.2. Case 2

Mr. B is a 70-year-old man with a history of dementia with Lewy bodies (DLB), a remote traumatic brain injury from playing football, and alcohol use disorder in sustained remission for 27 years. Medical history includes hypertension and osteoarthritis. At baseline, he was driving and living independently, with help from a visiting nurse, but with some known cognitive impairment. He was admitted after developing acute changes in mental status, including decreased speech output, word finding difficulties, and refusing to allow his visiting nurse into his house for the first time. On arrival he presented with right greater than left cogwheel rigidity (unclear how this compared to his baseline) and new myoclonus (left greater than right), observed by a neurology consultant. NCHCT at admission was notable for scattered hypoattenuating areas in the periventricular and subcortical white matter alongside generalized mild volume loss (both unchanged from prior imaging one year ago). Given some staring spells and speech arrest, a video EEG with long-term monitoring showed diffuse theta slowing, frequent and low amplitude isolated generalized discharges, and frequent brief periods of 1 Hz generalized rhythmic delta activity with sharp contouring and bifrontal predominance. On HD #2 he was noted to have a slight cough prompting SARS-CoV-2 PCR testing, which returned positive. He never manifested further respiratory symptoms or hemodynamic instability beyond a brief fever to 101.4 ˚F on HD #4. He had a persistently elevated CRP, with a maximum of 29.1 mg/L on HD #11. Psychiatry consultation was obtained on HD #11 given ongoing agitation and need for restraints despite medical stability. Exam at that time was notable for continued spontaneous myoclonus in his bilateral upper and lower extremities. He had minimal speech production beyond incoherent mumbling (which progressed to mutism over a few days), and he was restless to the point of having skin breakdown in multiple areas. LP and MRI of the brain were not obtained. He was started on as needed trazodone 25 mg with IM chlorpromazine 25 mg as a rescue for severe agitation (administered once on HD #11 and subsequently discontinued after resulting in diffuse rash surrounding injection site on his right lower extremity that resolved within three days). On HD #12 he was started on standing valproic acid 250 mg IV twice daily (BID) for agitation, and his home carbidopa-levodopa was held given inability to tolerate oral medications. These changes produced limited change in behavior. A lorazepam trial was pursued on HD #13 (1 mg IV) to treat possible catatonia given observed mutism and staring. This produced profound sedation without marked improvement (Bush-Francis Catatonia Rating Scale (BFCRS) reduced from 12 to 9 within 10 min of administration, with improvement noted in excitement and staring but no change to rigidity, mutism, or withdrawal). On HD #15 the dose of valproic acid was increased to 750 mg total daily dose after a trough level returned at 52.7 μg/mL. As of HD #18 he remained intermittently agitated and in a netbed but was noted to have improved speech production and had begun to swallow pills again. Carbidopa-levodopa was restarted.

2.3. Case 3

Mr. C is a 68-year-old man, under guardianship and residing in a group home, with a history of schizophrenia treated with clozapine and lithium for many years. He had one prior psychiatric hospitalization in 1988. Medical history includes chronic kidney disease stage 3, primary hyperparathyroidism, hypothyroidism, hypercholesterolemia, and

neurogenic bladder. At his baseline, the patient was polite with staff and other residents of the group home, talkative, though known to be impulsive (i.e. would sometimes rapidly consume food and end up aspirating). He initially presented after a witnessed fall with head strike and subsequent altered mental status. On exam, patient was unable to follow commands and had incomprehensible speech. Vital signs were within normal limits and he had no respiratory symptoms and a normal pulmonary exam. He was tested for SARS-CoV-2 given known exposure at his group home, and the PCR test returned positive. NCHCT demonstrated mild volume loss, mild small vessel ischemic changes, and a left-sided acute-on-chronic 7 millimeter (mm) subdural hematoma overlying the frontal, parietal, and temporal lobes with 3 mm left-to-right midline shift over the L frontal and parietal lobes. Chest CT showed ground-glass opacities in the right lung concerning for viral pneumonia. He was given levetiracetam for seizure prophylaxis and transferred to our institution for further care. Initial laboratory workup was notable for mild hypernatremia (sodium [Na] of 146), elevated creatinine (Cr) of 2.05, blood urea nitrogen (BUN) of 27, decreased carbon dioxide (CO2) of 21, and hypercalcemia (11.4). Urinalysis was concerning for acute cystitis and urine culture was positive for *Enterobacter*, so he was started on piperacillin/tazobactam. CRP was elevated, with a maximum value of 200.9 mg/L on HD #3. He was unable to safely take anything by mouth, so clozapine and lithium were held and psychiatry consultation was obtained on HD #2. On examination by the psychiatry consultant, he had almost no verbal output, was unable to follow commands, and was in four-point soft restraints with restless movements of arms and legs. He had mild oral tardive dyskinesia but no myoclonus or rigid tone. He was started on orally disintegrating olanzapine (7.5 mg) and IV haloperidol (2.5–5 mg) to manage agitation. EEG showed diffuse irregular delta slowing and frequent runs of generalized periodic epileptiform discharges. MRI was not obtained. The patient remained hypernatremic (Na peak of 160) throughout his hospital stay, though due to poor oral intake. He was in soft restraints until HD #7, when he began to consistently follow commands and his speech improved. He completed a 7-day course of levetiracetam for seizure prophylaxis. On HD #8, clozapine was re-initiated with plan to titrate back to home dose of 225 mg. He remained intermittently disoriented and impulsive for several days, at times being placed in 2-point soft restraints for safety, but was able to tolerate a dysphagia-diet. By HD #11 he was out of restraints and noted to be fully oriented and cooperative with all nursing care.

2.4. Case 4

Mrs. D is an 87-year-old woman living in a dementia unit at a skilled nursing facility (SNF) with a history of major neurocognitive disorder, unspecified type and major depressive disorder with psychotic features, for which she has been hospitalized multiple times (last in 2016) and which has been treated in the past with electroconvulsive therapy. Medical history includes chronic obstructive pulmonary disease (COPD), atrial fibrillation, diabetes mellitus type 2, a right bundle-branch block, coronary artery disease (s/p stent placement), aortic stenosis, and heart failure with preserved ejection fraction. At baseline, she is communicative and oriented to herself and situation. Home medications include mirtazapine 45 mg nightly, quetiapine 25 mg every morning and afternoon and 100 mg nightly, donepezil 5 mg daily, melatonin 5 mg nightly, and lamotrigine 25 mg daily. In the weeks leading up to admission, she was described by providers as anxious and dysphoric, which was attributed to the disruption in routine visits from family to her nursing facility due to COVID-19 isolation protocols. On the day of admission, she was noted to have a cough and was dyspneic, lethargic and not eating, prompting presentation to the emergency department. On arrival she was in atrial fibrillation with rapid ventricular response and hypervolemic. Vital signs were notable for persistent tachycardia to the 130's and normothermia. CRP was elevated with maximum value of 98.7 mg/L on HD #3, and ESR and fibrinogen were also elevated. NCHCT demonstrated no acute findings and no volume loss. Chest CT with contrast demonstrated cardiomegaly and enlargement of the pulmonary arteries without embolus, as well as peripheral ground glass opacities consistent with SARS-CoV-2 pneumonia. She was treated with metoprolol, furosemide, ceftriaxone and azithromycin and admitted to internal medicine. She was agitated in the emergency department, yelling and striking out at nurses, and received IM olanzapine 5 mg twice with improvement in agitation. On HD #2, she tested positive for SARS-CoV-2 via PCR (prompted by CT findings). She was also newly pancytopenic. For continued agitation, psychiatry was consulted on HD #2. Initial examination by the psychiatry consultant was notable for disorientation and preoccupation with physical symptoms, inattention, and mumbling, slurred speech. No myoclonus, rigidity, or alogia were present on initial psychiatric exam, though myoclonus was noted the following day. Her agitation was managed with intermittent soft restraints and IV haloperidol 1–2.5 mg IV q6h as needed for (PRN) agitation, later transitioned to quetiapine 25–50 mg q6h PRN agitation. Antipsychotic therapy reduced her agitation, but she remained disoriented and minimally interactive throughout the hospitalization. Her respiratory status continued to worsen in spite of continued treatment with antibiotics, nebulizers, and escalating oxygen supplementation. With her escalating oxygen requirement and admission code status as Do Not Resuscitate/Do Not Intubate, a decision was made by her care team and family to transition to Comfort Measures Only. The patient passed away on the afternoon of HD #5.

3. Discussion

3.1. Case discussion

Though these cases represent a heterogenous group of individuals and presentations, there are several features that are striking in their commonality across patients. Table 1 outlines the features shared between cases. Three of the four patients described here were men, and all were over age 65. All had underlying cognitive impairment, whether formally diagnosed as mild cognitive impairment or mild dementia, or informally noted by family members as memory loss or premorbid decline in functioning. These features suggest a vulnerable substrate, which may have been more susceptible to the insult of the virus.

It is also notable that many of the patients lacked other core features of COVID-19. In all 4 patients, changes in mental status were the primary manifestation of infection and the reason driving admission. Only 2 of the 4 patients had lung imaging findings consistent with COVID-19, and only 1 of them had prominent respiratory symptoms. No patients had GI symptoms. Two of the patients mounted no febrile response, and

Table 1
Clinical features of COVID-19 delirium.

	Change from baseline mental status	Agitation	Respiratory symptoms	Myoclonus	Rigidity	Abulia	Alogia	Elevated C-reactive protein	Rash
Case 1	+	+	−	+	+	+	+	+	+
Case 2	+	+	−	+	+	+	+	+	+
Case 3	+	+	−	−	−	+	+	+	−
Case 4	+	+	+	+	−	−	−	+	−

the other two had only very mild, transient fever. Importantly, however, all four patients had significantly elevated inflammatory markers, particularly CRP, which may be suggestive of a dysregulated immune response as a possible delirium precipitant.

A multifocal myoclonus was observed in all but one patient. This is perhaps not surprising, as myoclonus is a common feature of encephalopathy and is thought to generally signal global brain dysfunction, though it is notable that the myoclonus was more frequent and more apparent than would typically be observed in delirium and was present on initial exam in two patients. Notably, these same two patients also displayed increased muscle tone and rigidity. Of note given the motor findings, it has previously been observed that the basal ganglia is particularly sensitive to strongly neurotropic viruses, perhaps related to virally-induced autoimmune inflammatory response to basal ganglia antigens [8].

It is also worth noting that 2 of our patients developed an unusual unilateral livedoid rash of the lower extremity. While one of these occurred in the context of a chlorpromazine injection at the site, there have been reports of skin manifestations of COVID-19, including petechiae, morbilliform rash, erythematous rash, widespread urticaria, varicella-like vesicles, and pernio-like eruptions [9,10].

All patients stopped eating or taking anything by mouth at some point during the course of their illness. It is unclear whether this was due to anosmia or ageusia (patients were unable to answer questions about these symptoms) or due to general confusional state. The lack of oral intake has significant ramifications both in terms of nutritional and hydration status and with regard to medication options, especially around treatment of agitation.

Perhaps most striking, 3 of the 4 patients developed a progressive alogia during their hospital course, initially with paucity of speech and later with progression to complete mutism in some cases. This occurred rapidly, over a matter of hours to days, and progressed beyond the decreased interactivity that might be expected in hypoactive delirium. In conjunction with the loss of speech, patients also displayed a loss of spontaneous movement and in some cases developed a syndrome of abulia. Importantly, none of the patients demonstrated decreased speech output or immobility at baseline.

The presence of mutism combined with rigidity, withdrawal, and lack of spontaneous movement should prompt providers to consider whether patients may be manifesting the syndrome of catatonia. Notably, however, patients in this series appeared to lack any affective or motor features of the catatonia syndrome, and Gegenhalten rigidity was not observed. This raises the question of whether the symptoms may be more consistent with akinetic mutism, a phenomenon thought to be related to catatonia and typically associated with underlying brain injury involving midbrain-forebrain/medial frontal (mesolimbic) or midbrain-dorsolateral frontal (mesocortical) pathways. It is possible that the expression of classic catatonia involves the same mesencephalo-frontal system postulated for akinetic mutism [11]. Vulnerability to akinetic mutism may have been conveyed by the cessation of carbidopa-levodopa in Case 2 and by the exceptional pro-inflammatory state triggered by SARS-CoV-2 in all cases, which creates enormous immunometabolic demands that may impair the dopaminergic mesocorticolimbic pathways required for motivation and movement [12].

3.2. Putative explanations for delirium in SARS-CoV-2 infection

A major question remains whether delirium in COVID-19 represents a primary manifestation, heralding invasion of the brain by the virus, or whether it simply constitutes a secondary encephalopathy caused by inflammation or other systemic effects of the virus. Fig. 1 outlines possible mechanisms by which COVID-19 could cause delirium.

3.3. Primary neuro-invasive hypotheses

The possibility that some or all COVID-19-associated encephalopathies occur via the same hypothesized pathways as other (non-CNS) infectious and non-infectious causes (e.g. toxic/metabolic encephalopathy) cannot be discounted. However, there are two distinct proposed mechanisms for SARS-CoV-2 invading the CNS directly to cause a primary encephalopathy. Encephalitis, involving a 24-year-old man who experienced seizures following a week of worsening respiratory symptoms, has already been described [7]. Other neuropsychiatric symptoms are not well characterized in the report, but MRI with diffusion weighted images showed hyperintensity along the wall of the inferior horn of the right lateral ventricle, and fluid-attenuated inversion recovery (FLAIR) images showed hyperintense signal changes in the right mesial temporal lobe and hippocampus with slight hippocampal atrophy [7]. This is perhaps analogous to the situation with herpes simplex virus (HSV) encephalitis, which causes specific abnormalities in MRI and CSF analysis with positive CSF PCR testing that confirms the diagnosis. It is known that some coronaviruses, like SARS-CoV, appear capable of invading the brain via a synapse-connected chain extending from receptors in the lung to the medullary cardiorespiratory center [13]. It remains to be seen whether SARS-CoV-2 possesses this same capability and whether this contributes to acute respiratory failure in COVID-19 patients. Interestingly, however, in a sample of 7 patients with COVID-19 who manifested neuropsychiatric symptoms and were tested for SARS-CoV-2 in the CSF, none of them tested positive, indicating that neuropsychiatric symptoms do not require viral CNS invasion [2].

Another possible mechanism for primary encephalopathy is the ability of the virus to access the CNS directly via invasion of the olfactory bulb. This would be consistent with the observation of high rates of anosmia and ageusia, which are thought to represent involvement of the olfactory bulb [3]. Given the anatomical positioning, one could imagine the virus tracking along the olfactory bulb toward the uncinate fasciculus and reaching the anterior cingulate and basal forebrain directly via that pathway [14]. Of interest is the fact that several major neurocognitive disorders, including Alzheimer's disease and Parkinson's disease feature anosmia as a prominent early symptom as well. Perhaps even more pertinent with regard to possible neuro-COVID inflammatory effects is the finding that in both systemic lupus erythematosus (SLE) and systemic sclerosis patients, olfactory dysfunction is associated with age, neurocognitive dysfunction, inflammation and hippocampi and amygdalae volumes [15]. In SLE, the decrease in the sense of smell correlates with disease activity and CNS involvement [16].

3.4. Secondary systemic mechanisms

Potential mechanisms for a COVID-19-associated secondary delirium would include hypoxemia and oxidative stress resulting from ARDS, as well as hypoperfusion and uremia resulting from multi-organ failure in the setting of ARDS. As described in other cases, ARDS could also lead to DIC, resulting in a cerebrovascular accident [17]. Only the patient in Case 4 experienced symptoms that could be consistent with ARDS, however, and her delirium preceded worsening respiratory status. The pattern of older patients with pre-existing cognitive deficits being more susceptible would be consistent with higher vulnerability to metabolic encephalopathy seen in those with compromised substrates. The multifocal myoclonus is also common in delirium. Less common in toxic-metabolic encephalopathy, though, are the rigidity, progressive alogia, and abulia. The presence of these symptoms in many cases may point to a primary process involving the basal ganglia, motor and/or limbic cortex, and/or midbrain regions.

Another possibility is the development of a secondary encephalopathy caused by inflammatory cytokines crossing the blood-brain barrier (BBB). Such a cause of encephalopathy may still carry with it potentially valuable information about COVID-19. One extreme manifestation of this mechanism, already described in SARS-CoV-2 would be AHNE [5]. Though our cases were not consistent with AHNE

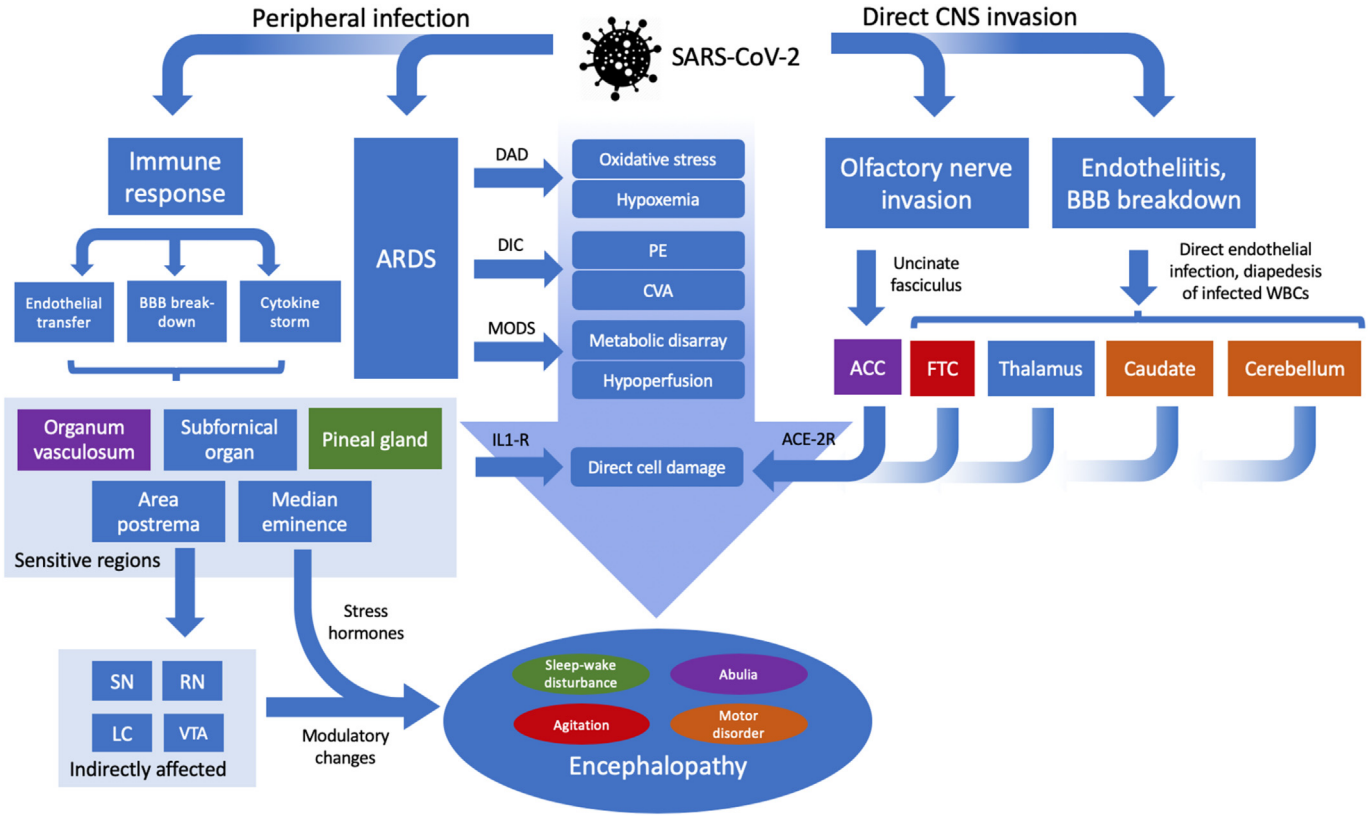

Fig. 1. Hypotheses of encephalopathy pathogenesis in COVID-19. Note that the model depicted below is hypothetical in nature and is meant to demonstrate the myriad ways in which SARS-CoV-2 infection may induce encephalopathy. For example, while a hallmark of COVID-19 is ARDS and associated hypoxemia, the mechanism of immune dysfunction in COVID-19 and its role in encephalopathy has yet to be established.
Abbreviations: SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2, IRS: immune reconstitution syndrome, BBB: blood-brain barrier, ARDS: acute respiratory distress syndrome, DAD: diffuse alveolar damage, DIC: disseminated intravascular coagulation, PE: pulmonary embolism CVA: cerebrovascular accident, MODS: multiorgan dysfunction syndrome (sepsis), IL1-R: interleukin-1 receptor, LC: locus coeruleus, VTA: ventral tegmental area, SN: substantia nigra, RN: raphe nucleus, ACC: anterior cingulate cortex, FTC: frontotemporal circuits.

based on available imaging, it is worth noting that the NCHCT findings in the report of AHNE were non-specific, and MRI was not obtained in any of our cases. Additionally, outside of AHNE, there are other syndromes that cause encephalopathy via the penetration of inflammatory cytokines into the subcortical regions. Perhaps the most well-known of these phenomena is the cytokine release syndrome, which can occur as a complication of chimeric antigen receptor T cell (CAR-T) therapy, and is well-known to lead to neuropsychiatric effects including delirium, language disturbances and seizures [18,19]. The high level of inflammatory markers seen in our cases suggests a significant systemic inflammatory response, which could lead to a cytokine storm, with BBB breakdown.

3.5. Hybrid model

A final possibility is a hybrid model, in which the virus may cause either a primary or secondary encephalopathy, or both. This combination would suggest similarity to human immunodeficiency virus (HIV), and, indeed, the parallels between some of the features described here and early experiences with HIV encephalopathy are striking. Olfactory dysfunction is among the primary deficits of HIV infection and occurs independently of disease stage. Studies confirm early work suggesting that odor thresholds are elevated early in HIV infection and the decline in olfactory identification and discrimination abilities is correlated with reduced cognitive abilities [20,21]. Symptoms such as myoclonus, progressive speech latency and alogia progressing to mutism, abulia and exquisite sensitivity to neuroleptics were common in the early days of the Acquired Immunodeficiency Syndrome (AIDS) epidemic and often signaled to providers invariable short-term demise [22,23]. The course often involved early symptoms of depression, apathy, decreased libido, and delirium marked by inattention and memory loss [22]. These symptoms were followed by speech latency and alogia with hypomimia, bradyphrenia, bradykinesia, abulia, tremor and frontal release signs, signaling the Miller Fisher mesencephalo-frontal disconnection syndrome [11,23]. Death quickly followed. If SARS-CoV-2 virus possesses neurotropic characteristics similar to HIV, and frontal-striatal areas of vulnerability are shared, the neuropsychiatric symptoms described in the cases above may be better understood.

The presumed pathophysiology of those CNS manifestations in HIV/AIDS may offer some insight into potential mechanisms for the symptoms observed in COVID. HIV is known to invade the circumventricular region via two mechanisms: direct and indirect invasion. The virus is able to directly enter the brain hitching a ride in infected macrophages that cross the BBB to replace the perivascular immune cells. Infected macrophages migrate into brain tissues and recruit microglia, which trigger a strong neuroinflammatory response syndrome that includes activated astrocytes. This process induces neuronal dysfunction and apoptosis. The circumventricular fenestrated endothelial areas represent the major thoroughfares for diapedesis of HIV-infected macrophages into the brain, and the regions abutting these areas determine the neuropsychiatric symptoms [24]. Invasion of the area postrema makes the patient vulnerable to depression and delirium due to selective vulnerability of midbrain neurotransmitter cell bodies, involvement of the pineal gland disrupts the sleep-wake cycle, and the organum vasculosum directly abuts the pregenual anterior cingulate

cortex, making the patient vulnerable to abulia/akinetic mutism [25].

Even in the absence of high viral load in the brain, however, a peripheral macrophage-initiated cascade of events in HIV can lead to secretion of proinflammatory cytokines and the generation of oxygen free radicals indirectly causing neuronal death and dysfunction [23,24]. This mechanism is similar to the cytokine storm or macrophage activation syndrome (MAS) hypothesis for SARS-CoV-2, and would potentially affect the same brain regions given the pathways for cytokines crossing the BBB [26].

In the case of SARS viruses and presumably SARS-CoV-2, the expression of the viral target receptor angiotensin-converting enzyme 2 (ACE2) in the brain and the nature of its interaction with the nicotinic acetylcholine receptor (nAChR) is crucial to understand more completely. The brain has been reported to express ACE2 receptors that have been detected in both neurons and glial cells [27], which makes them vulnerable to SARS-CoV-2 invasion [28]. ACE2 receptors are also expressed by endothelial cells, and endotheliitis has also been implicated in the pathology of the virus as a result of both direct and indirect mechanisms [29]. In HIV, macrophage-endothelial cell interactive pathogenesis contributed to breakdown of the BBB and predisposed patients to HIV encephalopathy [30]. If the SARS-CoV-2 virus enters the brain directly via disrupted circumventricular fenestrated endothelium or up an olfactory nerve track, we might expect a similar pathophysiological pathway to what we see in HIV encephalopathy. The fact that HIV can lead to a chronic, in addition to an acute encephalopathy, makes studying the role of the BBB in blocking direct viral entry to the brain an even larger priority in this SARS-CoV-2 pandemic.

3.6. Recommendations for workup and management of delirium in COVID-19

Diagnostic workup for patients with symptoms of encephalopathy who test positive for SARS-CoV-2 should include all of the usual myriad considerations for workup of altered mental status. Alterations in metabolic function, medication effects, hypoxemia, cardiac dysfunction, coagulopathy and hydration status deserve particular scrutiny. Additional questions around the utility of LP, MRI and EEG have arisen. While some authors suggest these as elements of a workup for all patients [31], this may not be practical due to tenuous clinical status, cost, exposure of staff, and resource availability (i.e., technicians to perform EEG or MRI scanners). MRI findings have been described in SARS-Co-V-2 patients with neuropsychiatric symptoms, including leptomeningeal enhancement and bilateral front-temporal hypoperfusion [2], though the specificity and consistency of these findings remains unclear. Furthermore, while a test for detecting virus in the CSF has been described in other countries [2,7], such a test is not yet available in the United States. EEG findings thus far appear to be nonspecific in nature and largely consistent with the diffuse background slowing expected in encephalopathy [2]. Further studies in this regard are necessary to direct best practices. In the meantime, we suggest a symptom-directed approach with particular focus on close discernment of signs of seizure, intracerebral hemorrhage, or other atypical neurologic findings to direct testing. Another compelling argument for the consideration of an MRI may be the desire for baseline imaging, given the concern for the virus to lead to a chronic encephalopathy if neurotropic. Finally, it is worth pondering whether autopsy should be considered in deceased patients with SARS-CoV-2 and delirium order to better elucidate parenchymal involvement in patients with and without neuropsychiatric symptoms.

Based on the available literature, it appears that a change in mental status or the presence of delirium should prompt testing for SARS-CoV-2. Prior case series have determined that 20–65% of patients with SARS-CoV-2 display features consistent with delirium, and our cases illustrate that mental status changes can occur as the presenting feature [2,6]. It would be prudent to advise hospitals, emergency rooms and outpatient clinics to expand testing criteria to include CNS manifestations, as has already been done at several institutions. Given emerging reports of new-onset psychosis with cognitive changes as another potential manifestation, it may also be worth considering testing in younger patients with an initial presentation of psychosis [32].

Management of neuro-COVID remains challenging. Based on our case series, delirium is often of the hyperactive or mixed variety, with high degrees of restlessness. Potential sensitivity to EPS with neuroleptic agents adds to the challenge, as does some indication of sensitivity to sedation. Due to concerns about EPS, low-potency antipsychotic agents may be preferred to manage agitation, including second-generation agents like olanzapine and quetiapine, but also chlorpromazine. IV and IM forms of chlorpromazine may also be particularly effective in patients exhibiting withdrawal who stop taking pills by mouth. While haloperidol carries theoretical risk of EPS, it is worth noting that the IV form is rarely associated with EPS, add haloperidol is now on the list of medications being studied as a treatment for SARS-CoV-2 because of its effects on sigma receptors [33]. Because medications like hydroxychloroquine and azithromycin, used in the management of COVID-19, have the potential to prolong the QT interval, particular attention should be paid to monitoring the electrocardiogram, calculating the QTc using a linear correction formula, and repleting electrolytes daily.

Based on anecdotal reports of success using dexmedetomidine in patients infected with SARS in the intensive care unit, alpha-2 agonists like clonidine may also be used to help manage agitation. Clonidine patches are easy to use and appear to be effective in some patients for decreasing restlessness. Side effects appear to be minimal, and pronounced hypotension has not been observed. While benzodiazepines are the mainstay of treatment for catatonia, they are not typically effective in akinetic mutism, and patients with delirium may be at increased risk for sedation and respiratory depression. Though not employed in this case series, an additional promising agent may be amantadine, which has a dual mechanism of action as an indirect dopamine agonist and *N*-methyl-D-aspartate (NMDA) antagonist. Amantadine has been shown to be effective for both akinetic mutism and catatonia [34,35], and may be a better option than stimulants, which were widely used for similar indications in the early days of AIDS, but have the potential to worsen delirium and psychosis [36].

We acknowledge the limitations of our approach. A small case series is obviously insufficient for elucidating complicated phenomenological and etiological elements of a new disease entity, especially in the neuropsychiatric domain. While these cases were consecutive, it is also worth mentioning that there were undoubtedly other cases of delirium in patients with SARS-CoV-2 for whom psychiatry was no consulted, and those cases may have had different features. However, at a moment in history when the world is overwhelmed by a pandemic, it is important to begin to make observations and identify hypotheses to be tested by rigorous scientific means as soon as possible, and to identify trends that may offer clinicians rational treatment consideration in the short run.

4. Conclusions

Delirium appears to be an important sequela of infection with SARS-CoV-2. In addition to the typical features of delirium, patients in our case series displayed significant agitation, increased tone or rigidity, abulia, alogia and evidence of significant systemic inflammatory response. This constellation of symptoms raises questions about whether the delirium seen in COVID-19 indicates simply a severe systemic illness in a vulnerable patient or whether SARS-CoV-2 may uniquely target subcortical structures via direct or indirect pathways, resulting in a syndrome of akinetic mutism. Further investigation is paramount in order to determine the potential CNS effects of infection with SARS-CoV-2. In the meantime, hospitals should consider adding mental status changes to the list of testing criteria, based on the current literature.

Author statement

S.B. conceived the manuscript and completed the bulk of the writing. N.P. created the Figure, revised the manuscript, and was in charge of references. C.H. and S.D. contributed cases and did substantial revising. F.M. contributed a case. G.F. helped write the section on pathophysiology. F.S. oversaw the process and completed the bulk of the editing.

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