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LETTER TO THE EDITOR

Catatonia in Hospitalized Patients With COVID-19: An Important Clinical Finding That Should Not be Missed

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Dear Editor,

Catatonia is an underrecognized fatal syndrome, with patients presenting with prominent motor and behavioral abnormalities due to underlying psychiatric or medical illnesses. Catatonia can occur in critically ill patients and has been reported in novel coronavirus disease (COVID-19) infection.[1,2] Herein, we report 4 cases of COVID-19-associated catatonia. We were given written consent to disclose the information reported.

Case 1 is a 25-year-old male patient with no prior medical illness. He was admitted with a seven-day history of fever, restlessness, disorientation, persecutory delusion, and insomnia. He tested positive for COVID-19 by reverse-transcriptase polymerase chain reaction (PCR) from a nasopharyngeal swab. Oral risperidone at 0.5 mg twice daily was prescribed to control his abnormal behavior. His mental status gradually worsened, and he was referred to neurology department two days later. Upon review, he was disorientated and had significant bilateral upper limb postural tremor. The following day, he deteriorated and became stuporous and immobile, with staring, mutism, and limb rigidity (Supplementary Video 1, segment 1 in the online-only Data Supplement). He was afebrile with no other features of autonomic dysfunction. Cerebrospinal fluid (CSF) analysis was normal, but he had rapidly declining renal function and elevated serum creatine kinase (> 7,800 U/L), suggesting malignant catatonia progressing to neuroleptic malignant syndrome (Table 1). Risperidone was withheld, and he was intubated and sedated with immediate dialysis support. Plasma exchange was initiated due to concern of immune-related encephalitis, but a limbic encephalitis antibody panel was not available. However, he developed sepsis with *Acinetobacter* pneumonia hindering further plasma exchange and, despite antibiotics, he succumbed to the infection.

Case 2 is a 51-year-old prisoner with schizophrenia and a history of marijuana abuse, who was admitted for COVID-19 infection. He had progressive bilateral lower limb stiffness one week prior to admission and was sent in from a local jail due to altered consciousness. He was treated with intravenous dexamethasone for his COVID-19 pulmonary infection, but his mental status did not improve. He was referred to neurology department on day eight of admission. Upon assessment, he was stuporous, immobile, not responding to painful stimuli, and had a pillow sign with rigidity of the upper and lower extremities (Supplementary Video 1, segment 2 in the online-only Data Supplement). A diagnosis of catatonia was made, and he was given oral clonazepam. Immunotherapy was not offered due to concern of superimposed bacterial lung infection on his chest CT scan. His brain MRI and CSF studies were normal (Table 1). Four days after clonazepam was titrated to 2 mg three times daily, he showed marked improvement in alertness and rigidity. He remained inpatient for an additional 14 days for rehabilitation. Clonazepam was tapered down and discontinued prior to discharge back to prison, with complete resolution of catatonia and recommencement of his antipsychotics for schizophrenia.

Case 3 is a 40-year-old female patient with no prior medical or psychiatric illness, who was admitted with an eight-day history of fever and cough. Her COVID-19 PCR from a nasopharyngeal swab was positive. She had difficulty sleeping for two

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Table 1. Summary of demographics and investigation findings of patients presenting with catatonia in COVID-19 infection

	Case 1	Case 2	Case 3	Case 4
Age/sex	26/male	52/male	40/female	67/male
Premorbid	No med problem	Smoker, marijuana, and amphetamine Underlying schizophrenia, on antipsychotics	None	Diabetes, hypertension, chronic kidney disease
COVID-19 nasopharyngeal swab PCR	Positive	Positive	Positive	Positive
Clinical presentation	Persecutory delusion, disorientation paranoia, restlessness, disorganized behavior (peed and sat on the floor) Rapidly progressed to stupor, staring, mutism, immobility, and limb rigidity	Progressive stiffness, walking difficulty one week prior to admission, progressed to stupor, mutism, food and drink refusal, severe rigidity, and pillow sign	Disorientated, food and drink refusal, shouting, and screaming with self-harm. Need physical restraint. Progressed to mutism, catalepsy, waxy flexibility, gegenhalten in the lower limbs	Mutism, negativism, food and drink refusal, gegenhalten sign involving upper and lower limbs
BFCRS	17	26	20	12
Day of COVID illness at onset of catatonia	8	17	17	19
Severity of COVID-19	Minimal lung involvement in CXR On nasal prong	Moderate lung involvement in CTPA	Minimal lung involvement in CXR On room air	Minimal Lung organising pneumonia in CTPA
Inflammatory markers	CRP 1.1 mg/L, LDH > 4,500 U/L, D dimer 3,437 ng/mL, ferritin 3,963 µg/L, CK > 7,800 U/L	CRP 9.4 mg/L, LDH 228 U/L, D dimer 3,344 ng/mL, ferritin 518 µg/L, CK 342 U/L	CRP 4.4 mg/L, LDH 514 U/L, D dimer 761 ng/mL, ferritin 397 µg/L, CK 396 U/L	CRP 9.4 mg/L, LDH 324 U/L, D dimer 569 ng/mL, CK 45 U/L
EEG	Not done	Diffuse slowing theta	Diffuse slowing theta to delta	Not done
CSF finding	Protein 0.27 g/L, glucose 6.6 mmol/L, acellular, culture neg, oligoclonal band neg, viral panel neg CSF COVID PCR not detected	Protein 0.27 g/L, glucose 4.0 mmol/L, acellular, culture neg, oligoclonal band neg, viral panel neg CSF COVID PCR not detected	Protein 0.25 g/L, glucose 5.2 mmol/L, acellular, oligoclonal band neg, viral panel neg CSF COVID PCR not detected	Not done
Immune panel	Not done	Serum paraneoplastic (Anti Hu, Ri, Yo, Ma, amphiphysin, CV2) and NMDAR neg	Serum paraneoplastic (Anti Hu, Ri, Yo, Ma, amphiphysin, CV2), NMDAR neg, anti-AMPA 1/2, anti-LGI1, anti-DPPX, anti-gamma-Aminobutyric acid-B neg	Not done
Brain imaging	CT brain normal	MRI brain normal	MRI brain normal	CT brain mild diffuse atrophy
Antipsychotics prior to developing catatonia	Risperidone 0.5 mg b.d., IM haloperidol p.r.n	None	Risperidone 0.5 mg b.d. 2 days Tab olanzapine 5 mg daily 4 days	None
Treatment initiated	Intubation, hemodialysis, plasma exchange × 1 cycle	Clonazepam 4 mg q.i.d. Baclofen 10 mg t.i.d.	Started on clonazepam titrating up to 2 mg b.d.	Started on clonazepam 1 mg t.i.d.
Outcome	Developed rhabdomyolysis, renal impairment, liver derangement Succumbed to severe sepsis and *Acinetobacter* pneumonia	Sign of improvement after 4 days of clonazepam	Sign of improvement after 5 days of clonazepam	Sign of improvement after 5 days of clonazepam
Duration of catatonia	-	11 days	12 days	14 days

COVID-19, coronavirus disease; PCR, polymerase chain reaction; BFCRS, Bush-Francis catatonia rating scale; CXR, chest X ray; CTPA, CT pulmonary angiogram; EEG, electroencephalogram; neg, negative; CRP, C reactive protein; LDH, lactate dehydrogenase; CK, creatine kinase; CSF, cerebrospinal fluid; NMDAR, N-methyl-D-aspartate receptor; AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; MRI, magnetic resonance imaging, IM, intramuscular; -, not available.

days prior to admission and was brought in for abnormal behavior with agitation, food refusal, persecutory delusion, and self-harm. She was given olanzapine 5 mg nightly from the start of her admission. Her CSF findings, brain MRI and autoimmune encephalitis panel were normal (Table 1). On day nine of admission, she became withdrawn with mutism, staring, pillow sign, limb rigidity, and waxy flexibility (Supplementary Video 1, segment 3 in the online-only Data Supplement). Antipsychotic treatment was immediately withheld; she was given clonazepam 2 mg twice daily with gradual recovery five days later. Her condition improved further with rehabilitation, and clonazepam was tapered off before she was sent home, with no recollection on the events that occurred during admission and the week prior.

Case 4 is a 67-year-old male patient with diabetes, hypertension, and chronic renal disease, who was admitted for COVID-19 infection presenting with a three-day history of cough, fever, and shortness of breath. He was intubated for acute respiratory distress syndrome and was mechanically ventilated for two weeks. He had minimal features of organizing pneumonia on chest CT; his prolonged ventilation was due to delayed recovery of mental status. Following extubation, he refused food and was noncommunicative. Although he had spontaneous voluntary limb movements, there was significant variable resistance during passive limb mobility, consistent with the gegenhalten sign (Supplementary Video 1, segment 4 in the online-only Data Supplement). He responded with clonazepam at 1 mg three times daily and had complete recovery two weeks later.

Catatonia is a psychomotor syndrome involving both motor and behavioral disturbances associated with many medical conditions, such as metabolic, autoimmune, and infectious conditions, as well as with numerous substances, and has been reported in COVID-19 infection.[1-4] The above four patients presented with catatonic symptoms of different severities (Supplementary Video 1 in the online-only Data Supplement). In the published literature, many of the patients had underlying psychiatric disorders, urging clinicians to have a high index of suspicion in these groups of patients (Supplementary Table 1 in the online-only Data Supplement). All patients had mild to moderate lung injury due to COVID-19. Two of the cases tested negative for anti-N-methyl-D-aspartate receptor receptor autoimmune encephalitis, a frequent cause of organic catatonia,[4] but inflammatory markers such as serum ferritin and C-reactive proteins were elevated (Table 1). CSF analysis, electroencephalography, and brain MRI imaging did not reveal any other potential etiologies of catatonia.

Various infections have been reported to cause catatonia and are postulated to be due to activation of the innate immune system[4] or alterations in gamma-Aminobutyric acid-ergic (GABAergic) and dopaminergic modulation of the cortico-basal ganglia-thalamo-cortical circuit.[1] Exposure to proinflammatory cytokines during the acute phase response has been associated with altered GABAergic transmission in the basal ganglia.[1,5] The use of antipsychotics may precipitate malignant catatonia, as illustrated in case 1; hence, a high index of suspicion should prompt immediate withdrawal of the dopaminergic blocking agent to avoid catastrophic outcomes. The first-line treatment is a benzodiazepine, which is a GABA agonist,[4] and our subsequent three patients had complete recovery after clonazepam without immunotherapy, suggesting that COVID-19-associated catatonia may be a transient syndrome precipitated by systemic proinflammatory cytokines. Intravenous methylprednisolone was used in several case reports in the treatment of catatonia (Supplementary Table 1 in the online-only Data Supplement).[3,6] It is important to differentiate this condition from akinetic mutism, which is a neurologic state of alertness without speech or movement resulting from irreversible medial prefrontal or midbrain injury.[7]

In conclusion, catatonia should be considered in patients with COVID-19-associated encephalopathy, as early detection can avoid iatrogenic sequelae of prescribing dopamine antagonists that will inadvertently provoke the malignant form of catatonia.

Ethics Statement

Written consent was obtained from patients for the publication of the information and videos shown in the manuscript. The manuscript has received approval for publication by the National Medical Research Register (NMRR) (RSCH ID-21-01312-RPD, NMRR ID-21-02414-MBT).

Supplementary Video Legends

Video 1. Segment 1: Case 1 was a 25-year-old man with COVID-19 infection who presented with stupor, immobility, staring, mutism, upper and lower extremity rigidity, and tremor. Segment 2: Case 2 was a 51-year-old prisoner infected with COVID-19 who developed mutism, rigidity, unresponsiveness to painful stimuli, abnormal limb posturing, and pillow signs. Segment 3: Case 3 was a 40-year-old woman who presented with rigidity, pillow sign, and waxy flexibility following COVID-19 infection. Segment 4: Case 4 was a 67-year-old gentleman with spontaneous limb movements but had significant variable resistance during passive limb mobility consistent with the gegenhalten sign.

Supplementary Materials

The online-only Data Supplement is available with this article at https://doi.org/10.14802/jmd.21172.

Conflicts of Interest

The authors have no financial conflicts of interest.

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Supplementary Table 1. Summary of COVID-19 associated catatonia reported in the literature

Publication	Age, sex	Premorbid	Clinical manifestation	Day of onset	Tests	Treatment	Outcome
Caan et al.[1]	43, M	None	Upper back pain & spasm, anxiety, insomnia progressed to stupor, mutism, withdrawal, staring, rigidity BFCRS 12	Day 15	CSF protein 32 mg/dL, acellular. MRI brain normal	IV lorazepam 1 mg t.d.s.	Residual psychomotor retardation & insomnia
Gouse et al.[2]	Elderly, M	Schizophrenia, COPD, interstitial lung disease, DM, HPT, AF, ET	Posturing, echolalia, mutism, staring, verbigeration, stereotypy, rigidity, waxy flexibility BFCRS 18	Day 9	Ferritin 1,400 ng/mL, CRP 85 mg/L, D dimer 1,200 ng/mL	Lorazepam	Demise
Vazquez-Guevara et al.[3]	43, F	None	Stupor silence, staring, apathy, slow thinking, decreased mobility, negativism, stiffness, gegenhalten sign BFCRS 19	PCR positive on day 2 admission	CRP 5.7 mg/L, CT brain normal EEG gen slow activity LP: OP 17, 16 mm^3 cell count, culture negative Limbic encephalitis panel not sent	IV MTP 1 g/day 5 days	Discharged Could walk and perform daily living activities
Zandifar and Badrfam[4]	61, M	Schizophrenia	Auditory hallucinations, delusion, paranoia, progressing to mutism, stupor, posturing, negativism, rigidity and seizure BFCRS -	Uncertain	NA	Lorazepam	Discharged with antipsychotics
Amouri et al.[5]	70, F	ESRF, DM, HPT, CAD, TIA, hypothyroidism	Immobility, mutism, grimacing, catalepsy, echolalia, stereotypy, rigidity, negativism, waxy flexibility, automatic obedience BFCRS 11	Day 16	Normal CT brain No CSF study	Lorazepam 0.5 mg t.d.s.	Discharged to rehabilitation facility
Deocleciano de Araujo et al.[6]	50, M	Childhood epilepsy, mild intellectual disability	Rigidity, negativism, withdrawal, BFCRS -	Day 18	Normal CT brain CK 8,819 U/L CSF protein 55 mg/dL	Sertraline 25 mg OD, olanzapine 5 mg OD, ECT	Fully recovered
Huarcaya-Victoria et al.[7]	23, F	None	Anxiety, insomnia, religious delusions, delusions of reference, auditory hallucinations, agitation, catalepsy, verbigeration BFCRS -	Day 3	NA	Olanzapine 15 mg OD	Discharged with olanzapine
Scheiner et al.[8]	50, F	HPT, osteoarthritis	Stupor, mutism, staring, mundane posturing, negativism, withdrawal BFCRS 11	Day 11	NA	Lorazepam	Recovered
	50, F	Schizophrenia, CKD	Mutism, withdrawal, staring, negativism BFCRS 12	Uncertain	NA	Lorazepam	Recovered
	20s, F	Bipolar disorder	Stupor, mutism, mundane, posturing, rigidity, negativism, withdrawal, paranoia BFCRS 14	Uncertain	NA	Lorazepam	Recovered
Torrico et al.[9]	36, F	HPT, DM, pancreatic mass	Irritable, immobility, mutism, refusal to eat most meals, staring behavior	Day 6	MRI brain normal CSF protein 103 g/dL, white cell 6/μL, EEG slowing 6 to 7 Hz Negative NMDAR and anti Hu antibodies CSF covid PCR negative	IV MTP 1 gm for 5 d Lorazepam 2 mg Haloperidol 5 mg Diphenhydramine 50 mg	Recovered
	64, F	Roux-en-Y gastric bypass, HPT, unspecific bipolar disorder	Staring, refusing food and drink, mutism		CSF normal & negative for anti NMDA, anti LGI1, anti-GAD 65, anti gamma-Aminobutyric acid-B, anti CASPR 2, Anti AMPA-R MRI brain normal, EEG normal	Lorazepam IV MTP 1 gm for 7 days	Discharged to skilled nursing facility
Kwon et al.[10]	62, F	HPT, schizoaffective, bipolar	Mutism, negativism, not responding to command BFCRS 13	Day 15	CT brain normal, MRI normal, EEG moderate diffuse cerebral dysfunction, no CSF study	1 mg lorazepam	Succumbed to massive PE

PCR, polymerase chain reaction; BFCRS, Bush-Francis catatonia rating scale; EEG, electroencephalogram; CRP, C reactive protein; LDH, lactate dehydrogenase; CK, creatine kinase; CSF, cerebrospinal fluid; NMDAR, N-methyl-D-aspartate receptor; AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; MRI, magnetic resonance imaging; DM, diabetes mellitus; COPD, chronic obstructive pulmonary disease; HPT, hypertension; AF, atrial fibrillation; ET, essential tremor; ESRF, end stage renal failure; CAD, coronary artery disease; TIA, transient ischemic attack; NA: not available; MTP, methylprednisolone; OD, once daily; ECT, electroconvulsive therapy; PE, pulmonary embolism.

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