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LETTER TO THE EDITOR

Encephalopathy and Complex Hyperkinesia in a Patient with Severe Acute Respiratory Syndrome Coronavirus-2 Infection

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Dear Editor,

In December 2019, several cases of atypical pneumonia were reported in Wuhan, China.[1] A zoonotic beta-coronavirus, severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), was identified as the causative agent.[2] Neurological complications have been reported during the ensuing worldwide pandemic, defined by the World Health Organization as the 2019 novel coronavirus disease (COVID-19). Filatov et al.[3] described COVID-19 encephalopathy with sharply contoured frontal waves on electroencephalography. Vollono et al.[4] reported focal status epilepticus (SE) in a SARS-CoV-2-infected patient. We describe a case of SARS-CoV-2 infection complicated by encephalopathy and transient, complex hyperkinesia.

A 74-year-old African American man was admitted to the Veterans Affairs Hospital in Lexington, Kentucky, after two days of nonpurulent cough, malaise, shortness of breath, and liquid stools. The medical history was notable for hypertension, diabetes mellitus, and chronic renal insufficiency. The patient was febrile (39°C), tachypneic, and tachycardic. Neurological examination revealed distal symmetric polyneuropathy. Admission laboratory studies showed mild anemia, thrombocytopenia, absolute granulocytosis and lymphocytopenia, and elevated serum creatinine (Supplementary Table 1 in the online-only Data Supplement). Testing for the viral genome of SARS-CoV-2 by a nasopharyngeal swab was positive, as was a fecal screen for *Clostridium difficile*. The patient was started on oral vancomycin.

On the fourth hospital day, the patient became acutely hypoxic and was intubated. Hydroxychloroquine and broad-spectrum antibiotics were started. Within 18 hours after intubation, the patient developed asynchronous myoclonic jerks of the extremities, which lasted for 10 minutes. Three hours later, multilimb myoclonic jerks recurred and persisted, despite boluses of benzodiazepine and intravenous (IV) loading of levetiracetam. With the patient lying supine, one side of the pelvis was observed to lift repetitively, followed by the same movement on the other side. The patient remained on midazolam infusion and was IV loaded with fosphenytoin, which caused the adventitious movements to abate. Hydroxychloroquine was discontinued.

A noncontrast CT scan of the brain showed no acute intracranial lesion, and a chest CT scan revealed pneumonia (Figure 1). The patient was treated empirically with IV acyclovir, ampicillin, ceftriaxone, and vancomycin. Two IV doses of tocilizumab were administered to treat the cytokine storm associated with SARS-CoV-2 infection. Lung-protective ventilation was initiated, with the patient alternating from supine to prone position. On the sixth hospital day, spinal fluid was obtained by lumbar puncture and showed no evidence of encephalitis (Supplementary Table 1 in the online-only Data Supplement). On the seventh day, worsening renal insufficiency prompted the initiation of hemodialysis by continuous renal replacement therapy (CRRT).

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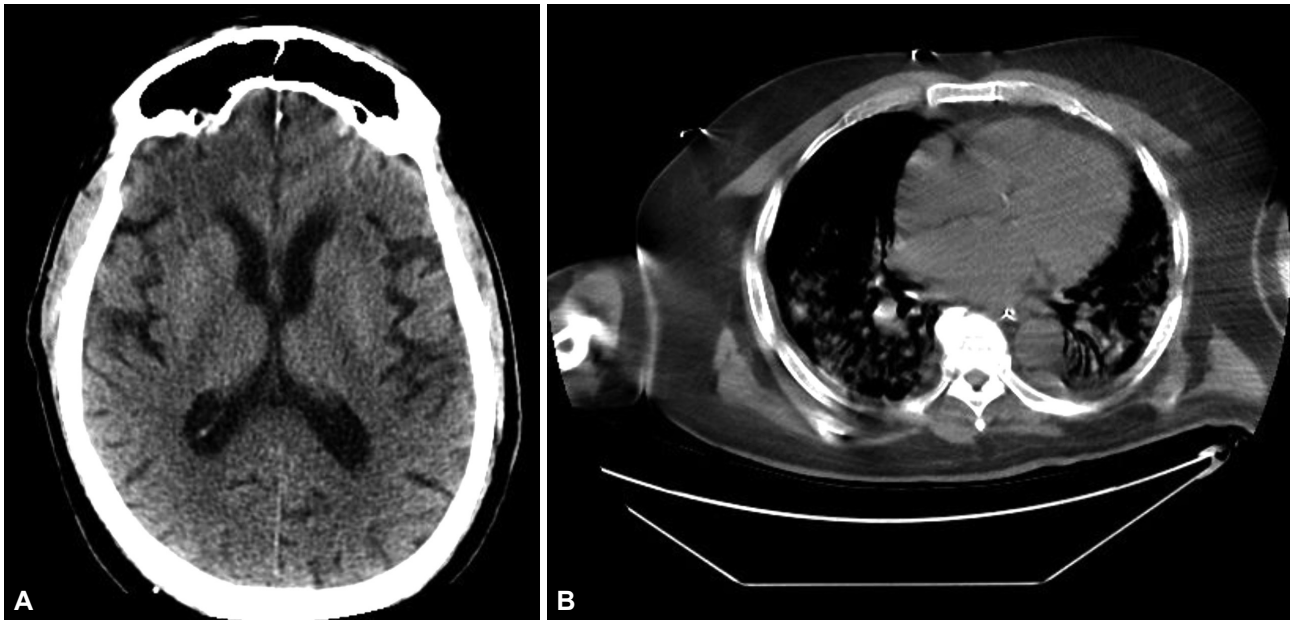

Figure 1. Noncontrast brain CT scan obtained on the 22nd hospital day, showing no infarct or hemorrhage within the deep gray nuclei and the thalami (A); noncontrast chest CT scan obtained on the 36th hospital day, revealing ground-glass opacities in the posterior region of the chest (B).

Lung-protective ventilation was halted.

On the 22nd hospital day, nonconvulsive SE was suspected. Conjugate gaze was deviated to the right. There were no observed adventitious movements. A brain CT scan was repeated with/without contrast and was unremarkable. Bedside electroencephalography revealed low-voltage, generalized slowing but no epileptiform activity.

The patient was re-examined on the 35th hospital day, 48 hours after sedation was withdrawn. Levetiracetam was discontinued in response to markedly elevated liver enzymes. The patient was able to visually attend and blink to threat but would not follow verbal commands. There was no gaze restriction or extraocular muscle palsy in the horizontal plane. There was no observed nystagmus or oculogyrus. The patient was noted to have few spontaneous movements of the upper limbs. Fasciculations were not identified. Biceps reflexes were graded as 1+/4+, bilaterally and symmetrically. In the lower limbs, the patellar reflexes were graded as 2+/4+ with sustained ankle clonus. Extensor plantar signs could not be elicited. A noncontrast brain CT scan was unrevealing.

The patient was observed to have intermittent facial dyskinesias, which included symmetric contractions of the frontalis muscles with eyebrow raising, forceful blinking, "fish-mouthing" with repetitive opening and closing of the lips, and puffing of the cheeks. The head would also laterally rotate to the right, and myoclonic contracture of the rectus abdominus muscles would occur. At intervals, the patient would engage in a complexly patterned motor activity that would begin with pelvic thrusting and splaying of the legs, followed by short bursts of repetitive myoclonic inversions of the knees (Supplementary Video 1 and 2 in the online-only Data Supplement).

One week later, the hyperkinetic movements lessened. The patient would attend visually and communicate by a head nod. The left arm was plegic and hyporeflexic. The fingers of the right hand were flexed, and the wrist extended in response to central nociception. There was increased motor tone in the legs, with crossed adduction of the knees and bilateral sustained ankle clonus.

During the prolonged hospitalization, the patient received IV infusions of methylprednisolone and high-dose dexamethasone. On the 43rd hospital day, the patient received an infusion of convalescent plasma donated by a COVID-19 survivor. On the 50th hospital day, the first of the two serial COVID-19 swabs tested negative. The patient was transferred to a rehabilitation facility on the 62nd hospital day.

Our patient developed febrile viral pneumonia due to SARS-CoV-2 infection, complicated by *C. difficile* colitis and acute-on-chronic renal insufficiency, which was corrected with CRRT. Admission laboratory studies revealed thrombocytopenia and lymphocytopenia, which have been observed in cases of severe SARS-CoV-2 infection.[5] Elevated creatine kinase levels indicated the potential for virally mediated muscle injury, a reported neurological complication of COVID-19.[5] As the infectious syndrome progressed in severity, our patient incurred rising levels of plasma D-dimer and ferritin, which have become recognized prognostic markers of a poor outcome.

This is the first report of encephalopathy with complex hyper-

kinesia as a neurological complication of SARS-CoV-2 infection. The complex hyperkinetic movements observed after the 35th hospital day appeared to follow marked elevations of plasma ferritin and CRP, considered biomarkers of the SARS-CoV-2-mediated cytokine activity. Rábano-Suárez et al.[6] reported three cases of generalized myoclonus in COVID-19 that appeared to occur temporally after viral-induced cytokine storms.

We concede that the first noted occurrence of repetitive myoclonic limb movements may have represented SE, as reported by Vollono et al.[4] The complexly patterned adventitious movements observed on the 35th hospital day were not epileptic; the myoclonic activity may have been caused by hepatic or renal encephalopathy. With hyporeflexia and bicrural paresis that affected the upper limbs after prone ventilation, we speculate that our patient experienced bibrachial neuritis and/or stretch injury to the brachial plexus, as reported by Diprose et al.[7]

Supplementary Video Legends

Video 1. In the video clip (1.08 minutes) obtained on the 45th hospital day, there is bilateral arm weakness with a wrist drop shown in the right limb. The patient engages in splaying movements of the legs, followed by short bursts of myoclonic knee adduction.

Video 2. In the video clip (50 seconds), there are magnified views of the myoclonic knee adduction.

Supplementary Materials

The online-only Data Supplement is available with this article at https://doi.org/10.14802/jmd.20084.

Conflicts of Interest

The authors have no financial conflicts of interest.

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Ethical Standards

All procedures performed in this study that involved a human participant were in accordance with the ethical standards of the institutional research committee and with the 1975 Declaration of Helsinki and its later amendments or comparable ethical standards. Informed consent was obtained from the legally authorized representative of the reported patient for journal publication.

Author Contributions

Conceptualization: Wenyang Li, Elif Pinar Coskun, Luther Creed Pettigrew. Data curation: Wenyang Li, Elif Pinar Coskun, Luther Creed Pettigrew. Formal analysis: Luther Creed Pettigrew. Funding acquisition: Luther Creed Pettigrew. Investigation: all authors. Methodology: Wenyang Li, Elif Pinar Coskun, Luther Creed Pettigrew. Project administration: Luther Creed Pettigrew. Resources: Luther Creed Pettigrew. Software: Luther Creed Pettigrew. Supervision: Luther Creed Pettigrew. Validation: Luther Creed Pettigrew. Visualization: Wenyang Li, Elif Pinar Coskun, Luther Creed Pettigrew. Writing—original draft: Luther Creed Pettigrew. Writing—review & editing: all authors.

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Supplementary Table 1. Laboratory data obtained during hospital admission

Laboratory data (normal range)	Hospital day								
	Pre-admission (-60 days)	Day 1 (admission)	Day 5	Day 6	Day 7	Day 22	Day 35	Day 50	Day 62 (discharge)
Hematology									
WBC, $\times10^3$/μL (5.0–10.0)	6.5	5.5	4.4	4.3	7.5	11.5	16.6	6.9	11.5
Hgb (g/dL)/Hct (%) (14–18)/(42–52)	14.4/44.2	13.9/43.0	12.6/39.7	11.2/35.5	11.9/37.9	7.0/22.2	7.4/23.8	8.7/28.8	7.7/25.1
Platelets, $\times10^3$/μL (150–450)	124	78	89	92	129	207	316	237	233
Absolute granulocyte, % (42–75)	65.8	77.6	72.2	67.1	85	-	86.4	67.7	-
Absolute lymphocyte, % (22–44)	24.1	15	24	28.1	11.1	-	5.9	17.3	-
Absolute granulocyte, $\times10^3$/μL (1.4–6.5)	4.25	4.25	3.19	3.19	6.37	-	14.3	4.68	-
Absolute lymphocyte, $\times10^3$/μL (1.2–3.4)	1.56	0.82	1.06	1.2	0.83	-	0.98	1.20	-
Coagulation									
PT (sec)/INR (11.5–14)/(0.91–1.16)	-	-	12.6/1.02	12.7/1.03	12.4/1.00	14.1/1.17	-	13.5/1.11	-
Activated PTT, sec (22.4–33.7)	-	-	-	-	34.2	-	-	-	-
Fibrinogen, mg/dL (224–537)	-	-	-	-	620	-	1,060	-	-
D-dimer, μg/mL FEU (plasma; 0–0.5)	-	-	3.43	3.77	2.69	3.7	4.66	-	-
Ferritin, ng/mL (plasma; 21.8–274.7)	-	-	2,913.8	4,051.3	4,622.2	1,779.9	2,431	-	-
Systemic inflammation/metabolism									
CRP, mg/L (plasma; 0–5.0)	-	-	173.4	224	160.7	28.3	264.5	-	-
Sedimentation rate, mm/hr (0–20)	-	-	-	49	-	-	-	-	-
ANA (serum; < 1:40)	-	-	-	-	-	-	-	< 1:40	-
c-ANCA (serum; < 1:20)								< 1:20	-
p-ANCA (serum; < 1:20)								< 1:20	-
Metabolism and nutrition									
Hgb A1c, % (4.4–6.4)	9.0	-	-	-	-	-	-	-	-
LDH, U/L (125–220)	-	-			-	500	634	-	-
CK, IU/L (plasma; 30–200)	-	-	349	321	-	-	59	-	-
Lactic acid (plasma; 0.5–2.2)	-	-	-	-	-	-	0.7	-	-
Vitamin B12, pg/mL (plasma; 213–816)	-	-	-	-	-	1693	-	-	-
Vitamin B1, nmol/L (whole blood; 66.5–200)	-	-	-	-	-	90.8	-	-	-
Vitamin D 25-hydroxy, ng/mL (serum; 30–100)	-	-	-	-	-	16.9	-	-	-
Renal function									
Blood urea nitrogen, mg/dL (serum; 9–25)	25	26	59	70	80	66	77	56	47
Total creatinine, mg/dL (serum; 0.72–1.25)	1.8	2.05	3.55	5.05	6.6	2.94	2.33	1.81	2.3
eGFR, mL/min/1.73 m^2 (> 60)	45	39	20	14	10	25	33	45	34
Liver function									
Total bilirubin, mg/dL (0.2–1.2)	0.3	0.9	0.4	0.3	0.2	0.4	2.2	2.2	1.2
Direct bilirubin, mg/dL (0–0.5)	-	0.3	0.3	-	-	0.3	1.9	1.6	-
AST, U/L (5–34)	35	43	83	71	58	138	387	216	124
ALT, U/L (0–55)	32	35	47	40	32	343	571	400	230
Alkaline phosphatase, U/L (40–150)	75	55	47	45	44	311	698	1,257	943
Ammonia, μmol/L (plasma; 18–72)	-	-	-	-	-	48	-	-	-
Infectious disease									
COVID-19 screen PCR (naso-pharyngeal swab)	-	Positive	-	-	-	Positive	Positive	Negative	-
Influenza A PCR (naso-pharyngeal swab)	-	Negative	-	-	-	-	-	-	-
Influenza B PCR (naso-pharyngeal swab)	-	Negative	-	-	-	-	-	-	-
Respiratory syncytial virus (naso-pharyngeal swab)	-	Negative	-	-	-	-	-	-	-
MRSA (nares)	-	Negative	-	-	-	-	-	-	-
Hepatitis B (serum)	-	-	-	-	-	-	Not detected	-	-
Hepatitis B surface antigen	-	-	-	-	-	-	Not detected	-	-
Hepatitis C	-	-	-	-	-	-	Not detected	-	-
CMV IgG (serum)	-	-	-	-	-	-	-	Positive	-
CMV IgM (serum)	-	-	-	-	-	-	-	Negative	-
HIV Ab/Ag screen (serum)	-	-	-	-	-	-	Negative		
Aerobic/anaerobic blood cultures	-	No growth at 48 hrs	No growth at 48 hrs	-	-	-	-	-	-
Spinal fluid									
Cell count	-	-	-	5 nucleated cells/μL (99% mono)	-	-	-	-	-
Protein, mg/dL (15–45)	-	-	-	49	-	-	-	-	-
Gram stain/India ink stain	-	-	-	Negative	-	-	-	-	-
Bacterial culture	-	-	-	Negative	-	-	-	-	-
Meningitis/encephalitis panel	-	-	-	Negative	-	-	-	-	-
Fungal culture	-	-	-	No growth × 1 week	-	-	-	-	-
Cryptococcal Ag screen	-	-	-	Negative	-	-	-	-	-
Viral culture	-	-	-	No growth × 1 week	-	-	-	-	-
HSV-1/2 DNA (PCR)	-	-	-	Negative	-	-	-	-	-

WBC: white blood cell, PT: prothrombin time, INR: International Normalized Ratio, PTT: partial thromboplastin time, CRP: C-reactive protein, LDH: lactate dehydrogenase, CK: creatine kinase, ANA: anti-nuclear antibody, c-ANCA: cytoplasmic anti-neutrophil cytoplasmic antibodies, p-ANCA: perinuclear anti-neutrophil cytoplasmic antibodies, eGFR: estimated glomerular filtration rate, AST: aspartate aminotransferase, ALT: alanine transaminase, COVID-19: 2019 novel coronavirus disease, PCR: polymerase chain reaction, MRSA: methicillin-resistant *Staphylococcus aureus*, CMV: cytomegalovirus, HIV: human immunodeficiency virus, HSV: *Herpes simplex* virus.