ARTICLE

Acute hypokinetic-rigid syndrome following SARS-CoV-2 infection

Antonio Méndez-Guerrero, MD, María Isabel Laespada-García, MD, Adolfo Gómez-Grande, MD, Mariano Ruiz-Ortiz, MD, Víctor Antonio Blanco-Palmero, MD, Francisco Javier Azcarate-Diaz, MD, Pablo Rábano-Suárez, MD, Eva Álvarez-Torres, MD, Carlos Pablo de Fuenmayor-Fernández de la Hoz, MD, Diana Vega Pérez, MD, Raquel Rodríguez-Montalbán, MD, Alfredo Pérez-Rivilla, MD, Javier Sayas Catalán, MD, Ana Ramos-González, MD, PhD, and Jesús González de la Aleja, MD, PhD

Correspondence
Dr. Méndez-Guerrero
mendezguerrero.antonio@gmail.com

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Abstract

Objective

To report a case of a patient infected with severe acute respiratory syndrome coronavirus 2 (SARS–CoV-2) who acutely developed a hypokinetic-rigid syndrome.

Methods

Patient data were obtained from medical records from the Hospital Universitario 12 de Octubre in Madrid, Spain. [^{123}I]-ioflupane dopamine transporter (DaT) SPECT images were acquired 4 hours after a single dose of 185 MBq of ^{123}I-FP-CIT. Quantitative analysis was performed with DaTQUANT software providing the specific binding ratio and *z* score values of the striatum.

Results

We report a previously healthy 58-year-old man who developed hyposmia, generalized myoclonus, fluctuating and transient changes in level of consciousness, opsoclonus, and an asymmetric hypokinetic-rigid syndrome with ocular abnormalities after a severe SARS–CoV-2 infection. DaT-SPECT confirmed a bilateral decrease in presynaptic dopamine uptake asymmetrically involving both putamina. Significant improvement in the parkinsonian symptoms was observed without any specific treatment.

Conclusion

This case study provides clinical and functional neuroimaging evidence to support that SARS–CoV-2 can gain access to the CNS, affecting midbrain structures and leading to neurologic signs and symptoms.

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From the Departments of Neurology (A.M.-G., M.I.L.-G., M.R.-O., V.A.B.-P., F.J.Z.-D., P.R.-S, C.P.d.F.-F.d.l.H., J.G.d.l.A.), Nuclear Medicine (A.G.-G., D.V.P.), Anesthesiology (E.A.-T., R.R.-M.), Microbiology (A.P.-Z.), Pneumology (J.S.C.), and Neuroradiology (A.R.-G.), Hospital Universitario 12 de Octubre, Madrid, Spain.

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Glossary

CoV = β-coronavirus; **COVID-19** = coronavirus disease 2019; **DaT** = dopamine transporter; **SARS–CoV-2** = severe acute respiratory syndrome coronavirus 2.

At the end of 2019, a cluster of cases of pneumonia were reported in Wuhan, China.[1,2] A novel β-coronavirus (CoV), subsequently called severe acute respiratory syndrome coronavirus 2 (SARS–CoV-2), was identified as the causative agent of the disease, called coronavirus disease 2019 (COVID-19).[1]

Several studies have provided evidence for the neuroinvasive potential of almost all β-CoV,[3] including SARS-CoV,[4] with which SARS–CoV-2 shares high structural similarity.[5] Neurologic features in COVID-19 may be relatively common.[6] Given that detailed neurologic examinations are difficult to perform in an epidemic, some neurologic signs and symptoms may have been previously overlooked.[6]

We report here a patient who developed hyposmia, transient generalized myoclonus and tremor, fluctuating and transient changes in his level of consciousness, intermittent opsoclonus, and finally an asymmetric hypokinetic-rigid syndrome with ocular abnormalities after a severe SARS–CoV-2 infection. In some aspects, this syndrome might resemble von Economo encephalitis lethargica,[7] a disease for which a viral etiology has long been presumed.[8]

Methods

Patient data were obtained from the medical records of Hospital Universitario 12 de Octubre in Madrid, Spain. The study was approved by the local ethics committee/institutional review board. The patient provided written informed consent.

Dopamine transporter (DaT)-SPECT image analysis was performed with DaTQUANT software (GE Healthcare, Chicago, IL), providing the specific binding ratio and *z* score values of the striatum.

Standard protocol approval, registration, and patient consent

Written informed consent was obtained from the patient participating in the study (consent for research).

Data availability

The data supporting the findings of this study are available within the article.

Results

A 58-year-old right-handed man presented to the emergency department with a 7-day history of dry cough, fever, nausea, and shortness of breath. His medical history was remarkable for hypertension and dyslipidemia, which were controlled with enalapril and simvastatin. On admission, he had a fever (38.7°C) and mild tachypnea. His level of oxygen saturation was 89% while breathing ambient air. Laboratory test results are shown in table 1. Chest radiography revealed bilateral diffuse patchy infiltrates. A nasopharyngeal swab was positive for SARS–CoV-2 in a real-time reverse-transcription PCR assay. He was started on empirical treatment as shown in figure 1.

By day 10 after the onset of symptoms, dyspnea worsened. The patient was transferred to the intensive care unit, and mechanical ventilation was initiated. He required a tracheostomy for prolonged ventilation.

After 23 days of mechanical ventilation with no major respiratory issues, the patient was finally weaned from the ventilator. Bilateral and synchronous myoclonic jerks were observed, involving predominantly the distal upper limbs. Myoclonus was present at rest and was aggravated by both postural changes and movements but not by tactile or auditory stimuli. Superimposed mild postural tremor was also noted. The complete blood test showed no metabolic abnormalities. An EEG demonstrated no ictal or interictal epileptiform discharges. Myoclonus spontaneously resolved without specific treatment.

Two days later, on day 36, he suffered a transient episode of decreased consciousness. This episode was not acute. It lasted several hours and was not accompanied by neurologic deficits or abnormal movements. Respiratory and cardiac monitoring showed no relevant events. Laboratory tests, cranial CT scan, and CT angiogram showed no abnormalities. Because the patient was stable with acceptable oxygenation levels, there was no need for reinstituting mechanical ventilation. A new EEG was performed, showing diffuse mild and reactive slowing without any asymmetries or epileptiform discharges. A few hours later, the patient experienced another episode of decreased consciousness; he became reactive only to painful stimuli and presented roving eye movements. Bilateral myoclonus in both upper extremities was elicited when the patient was alerted. Brief conjugated, multidirectional, and chaotic saccadic ocular movements compatible with opsoclonus were also observed. Brain MRI results were normal. A systemic examination was performed during the episodes, and the results were unremarkable. He recovered gradually during the subsequent hours.

Once the patient recovered, a detailed neurologic examination was performed. He was aware, and no attention, language, or memory deficits were noted. Nonstandardized olfactory

Table 1 Main laboratory values during the course of illness[a]

Variable	Reference range	Day of illness							
		7	10	18	28	33	36	39	49
Red cell count (per 1 μL), n	4,200,000–5,600,000	5,430,000	5,580,000	4,840,000	3,520,000	3,990,000	4,4160,000	4,120,000	4,760,000
White cell count (per 1 μL), n	4,000–11,300	10,300	8,000	13,400	8,800	10,400	5,900	7,100	6,200
Absolute neutrophil count (per 1 μL), n	1,800–7,400	7,700	6,800	11,700	6,400	8,000	4,700	5,300	4,500
Absolute lymphocyte count (per 1 μL), n	1,200–4,000	1,500	900	700	1,400	1,200	1,000	1,000	1,100
Hemoglobin, g/dL	13.0–16.80	16.3	16.5	14.2	10.7	12.0	12.9	12.6	13.8
Platelets count (per 1 μL), n	140,000–450,000	183,0000	199,000	240,000	219,000	185,000	180,000	217,000	226,000
Sodium, mmol/L	136–145	137	139	151	143	137	140	141	142
Potassium, mmol/L	3.5–5.10	3.79	3.87	3.29	3.85	3.71	3.34	3.52	3.64
Calcium, mg/dL	8.6–10.2	—	8.5	8.2	9.0	8.8	8.1	8.4	8.9
Glucose, mg/dL	70–110	115	122	316	128	120	116	101	107
Creatinine, mg/dL	0.7–1.2	0.75	0.66	0.64	0.46	0.39	0.52	0.54	0.50
Magnesium, mg/dL	1.6–2.6	1.8	—	2.1	—	—	2.18	—	—
Blood urea nitrogen, mg/dL	9–23	—	—	—	—	20.09	21.02	—	—
Total protein, g/dL	6.4–8.3	7.4	7.1	5.7	4.7	5.9	6.4	6.1	6.2
Albumin, g/dL	3.5–5.0	4.1	3.7	3.4	2.7	3.5	2.8	4.1	4.0
Alanine aminotransferase, U/L	5–45	27	84	48	49	84	25	60	48
Aspartate aminotransferase, U/L	5–33	37	99	21	33	50	40	27	19
γ-Glutamyl transferase, U/L	8–61	187	322	320	549	631	53	185	154
Alkaline phosphatase, U/L	40–130	106	182	82	101	125	54	82	73
Total bilirubin, mg/dL	0.2–1.0	0.6	1.3	2.1	1.1	0.8	0.4	0.9	0.9
Lactate dehydrogenase, U/L	135–225	339	539	353	289	360	461	254	233
Creatine kinase, U/L	34–171	—	167	56	542	298	28	—	—
Ammonium, μmol/L	10–55	—	—	—	—	27	28	—	—
Ferritin, ng/mL	30–400	1,520	—	—	1,483	—	—	—	—
C-reactive protein, mg/dL	0.10–0.50	5.95	10.46	0.04	0.05	0.07	0.06	0.04	0.05

Continued

Table 1 Main laboratory values during the course of illness[a] *(continued)*

Variable	Reference range	Day of illness							
		7	10	18	28	33	36	39	49
Procalcitonin, ng/mL	≤0.50	—	0.2	0.18	—	0.04	0.03	—	—
Prothrombin activity, %	75–140	67	63	76	83	72	42	62	71
D-dimer, ng/mL	0–500	615	760	5,820	7,526	3,126	4,256	2,985	525
Pao_2/Fio_2 ratio, mm Hg)	>300	285	185	302	367	379	380	384	452
Carbon dioxide, mmol/L	25–35	39	38	74	33	38	42	35	—
Arterial lactate, mmol/L	1–1.5	1.8	2.3	2	1.2	1.2	1.3	0.6	—

[a] To convert the values for calcium to millimoles per liter, multiply by 0.250. To convert the values for creatinine to micromoles per liter, multiply by 88.4. To convert the values for blood urea nitrogen to millimoles per liter of urea, multiply by 0.357. To convert the values for total bilirubin to micromoles per liter, multiply by 17.1.

testing showed moderate hyposmia. He had a slight up-gaze restriction. Vertical saccades were produced by moving his eyes in a lateral arc ("round the houses" sign). Smooth pursuit was impaired. Spontaneous intermittent opsoclonus was observed in the primary gaze position. Examination of the remaining cranial nerves was normal. He had a mild proximal tetraparesis (4+ of 5 on the modified Medical Research Council scale). Muscle stretch reflexes were brisk. Normal flexor plantar reflexes were observed. Sensory examination showed no abnormalities. The most remarkable finding was a right side–dominant hypokinetic-rigid syndrome, with mixed postural and resting tremor. Loss of spontaneous movement and moderate cogwheel rigidity enhanced with the Froment maneuver were noticed. Frank hypomimia with diminished blinking and the glabellar tap sign were also elicited (video 1).

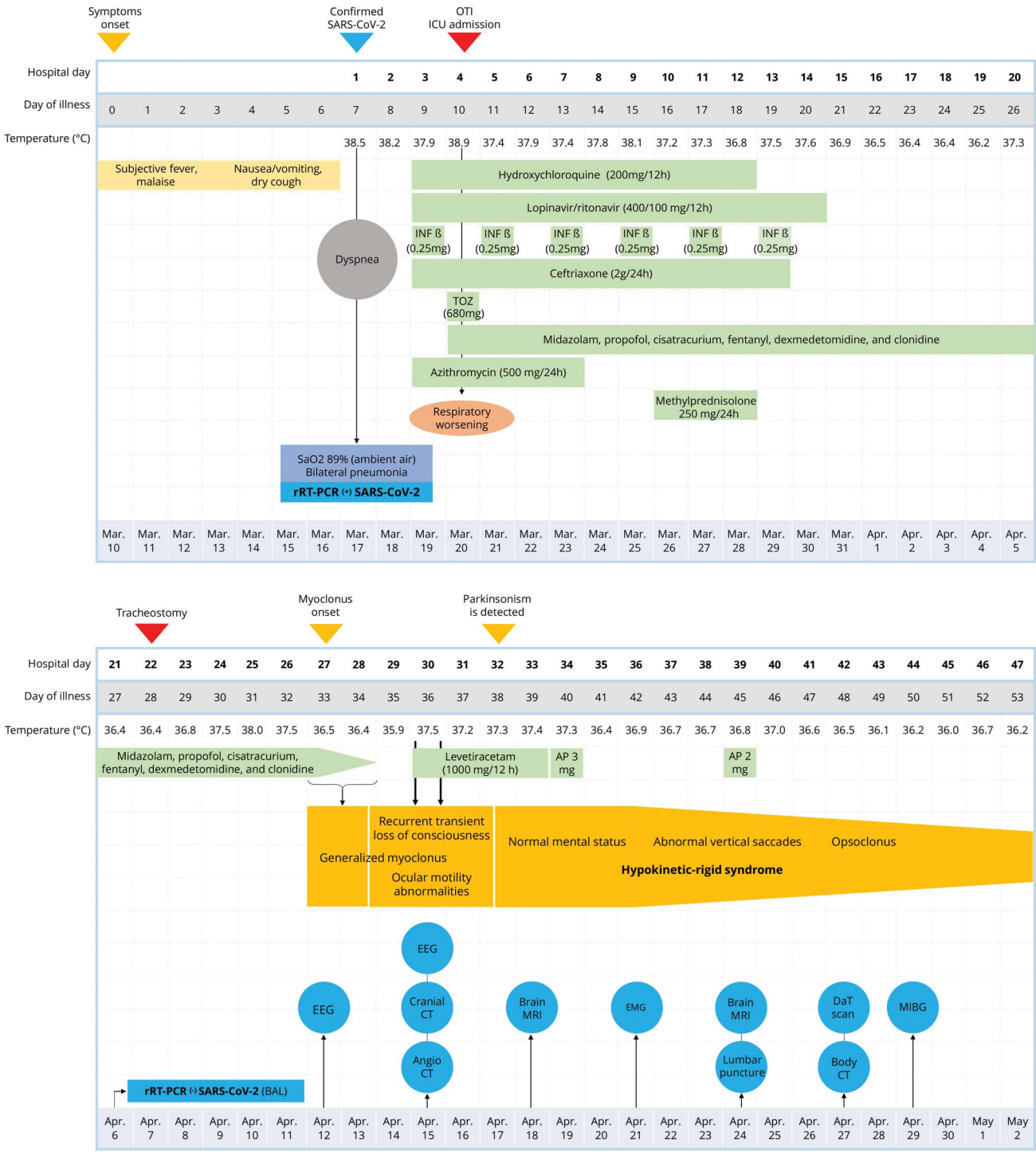
At this stage, no drugs known to cause acute parkinsonism were reported or administered (figure 1). The patient had no family history of tremor or parkinsonism. Hyposmia, constipation, REM sleep behavior disorder, and other premorbid parkinsonian symptoms were also absent before infection. An extensive laboratory workup, including CSF analysis (table 2) and repeated contrast-enhanced MRI (figures 2–3), revealed no abnormalities. An [^{123}I]-ioflupane DaT-SPECT showed a bilateral decrease in presynaptic dopamine uptake asymmetrically involving both putamina (figure 4) and was worse on the left side. A SPECT ^{123}I-metaiodobenzylguanidine myocardial scintigraphy scan ruled out cardiac autonomic denervation. An electrodiagnostic study was performed 42 days after the onset of symptoms and showed findings consistent with a mild critical illness polyneuromyopathy. It also revealed a resting tremor of the upper extremities that had a frequency of 7 Hz (figure 5).

On day 40, the apomorphine test (3 mg) induced nausea, vomiting, and severe drowsiness. The test was repeated 5 days later using 2 mg of the drug, but no clinical responses were observed. Significant improvement in tremor, rigidity, and bradykinesia was observed without any specific treatment (video 1). At the time of the writing of this report, general recovery and parkinsonism improvement allowed the patient to take a few steps without support.

Discussion

We report a case of asymmetric hypokinetic-rigid syndrome with mild resting and postural tremor, vertical oculomotor abnormalities, and opsoclonus associated with hyposmia. This condition developed after a severe SARS–CoV-2 infection and a period of transient impaired consciousness and generalized myoclonus. This combination of signs and symptoms suggested the involvement of basal brain structures. The DaT-SPECT results demonstrated an asymmetric loss of integrity in the terminal fields of the nigrostriatal neurons. After a comprehensive workup, no etiology other than COVID-19 was found. A striking spontaneous improvement was documented without any specific therapy.

Figure 1 Clinical course and temporal pattern of the key events



Main clinical events, diagnostic tests performed, and treatments administered. AP = apomorphine; BAL = bronchoalveolar lavage; DaT-SPECT = dopamine transporter SPECT; ICU = intensive care unit; IFN = 1ß interferon beta-1b; MIBG iodine 123 = ^{123}I-metaiodobenzylguanidine; OTI = orotracheal intubation; rRT-PCR = real-time reverse transcription PCR; Sao2 = oxygen saturation; SARS–CoV-2 = severe acute respiratory syndrome coronavirus 2; TOZ = tocilizumab.

More than a century ago, Constantin von Economo[7] published the first cases of encephalitis lethargica. As in the case we describe here, during the acute phase, patients typically experienced excessive sleepiness, ocular motility disorders, and movement disorders (such as myoclonus or rigidity), sometimes with day-to-day changes in symptomatology.[8] The chronic phase, with postencephalitic parkinsonism, was observed years later.[8] Since then, scientists have attempted to link some viral infections to movement disorders such as Parkinson disease.[9–11] Postencephalitic parkinsonism has been reported after infection with certain viruses that can involve the substantia nigra.[10] Although parkinsonism has not

Table 2 Specific tests for acute-onset parkinsonism study

Thyroid function (TSH, T4)	Normal
Parathyroid hormone	Normal
Vitamin B_{12}	Normal
Folic acid	Normal
Serologies (HIV, HBV, HVC, syphilis, *Mycoplasma pneumoniae*)	Negative
Serum copper	Normal
Ceruloplasmin	Normal
Autoimmune disorders screening	
Non–organ-specific autoimmune disorders[a]	Negative
Onconeuronal and antineuronal surface antibodies[b]	Negative
Other (anti-GAD65 and anti-thyroid antibodies[c])	Negative
CSF analysis	
Basic biochemistry and white cell count	Glucose 61 mg/dL (40–70) (blood glucose 92 mg/dL); protein 0.82 g/L (0.15–0.45); white cell count 8 cells/μL (0–10)
Microbiological studies[d]	Negative
CSF IgG index	0.47 (no intrathecal IgG synthesis)
Oligoclonal bands	Negative
Onconeuronal and antineuronal surface antibodies	Negative
Contrast enhanced CT scan of the chest, abdominal, and pelvis	Chest CT scan showing bilateral peripheral ground-glass opacifications involving lower lobes, with an area of consolidation in left lung Abdominal and pelvic organs were normal

Abbreviations: HBV = hepatitis B virus; HCV = hepatitis C virus; IgG = immunoglobulin G; T4 = thyroxine; TSH = thyroid-stimulating hormone.
[a] Antibodies: antinuclear, anti-DNA, anti-SSA/Ro, anti-SSA/Ro52, anti-SSA/Ro60, anti-SSB/La, anti-RNP68, anti–centromere protein B, anti-TOPO-1/SCL-70, anti-JO-1/HRS, anti–ribosomal P, anti-Sm, anti–SM-RNP, anti-chromatin, anti-myeloperoxidase, and anti-proteinase3.
[b] Encephalitis profile: anti-NMDAR, anti-CASPR2, anti-AMPAR1/R2, anti–LGI-1, anti-DDPX, anti-GABAbR, and IgLON5. Onconeuronal antibodies: anti-GAD65, anti-SOX1, anti.Ma-1, anti.Ma-2, anti-amphiphysin, anti-CV2, anti-Ri, anti-Yo, and anti-Hu.
[c] Anti-thyroid antibodies: anti-thyroid peroxidase antibodies, antithyroglobulin antibodies, and anti-TSH receptor antibodies.
[d] Microbiological studies: Gram staining and bacterial/fungal cultures; PCR assays for detection of severe acute respiratory syndrome coronavirus 2, *Tropheryma whipplei*, *Mycoplasma pneumoniae*, Enterovirus, and Herpes simplex virus 1 and 2; and Venereal Disease Research Laboratory test for syphilis.

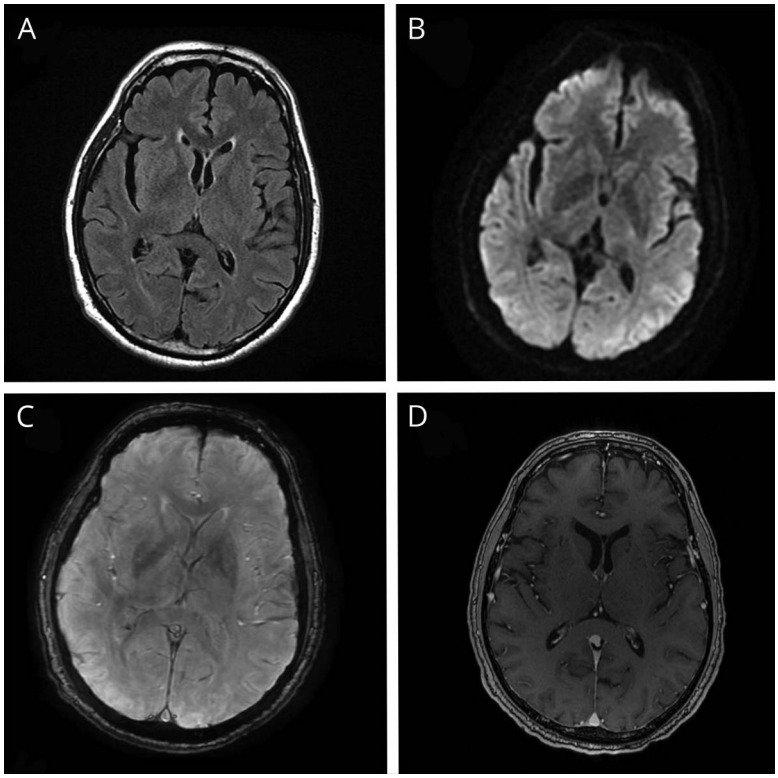
been described in association with coronavirus outbreaks,[10] anti-CoV antibodies have been identified in the CSF of individuals with Parkinson disease.[12]

SARS-CoV and other coronaviruses have the potential to be neuroinvasive in humans.[4,13,14] Experimental studies have shown that when inoculated intranasally, coronaviruses[15,16] and other respiratory viruses such as H1N1[17] and H1N5[11] spread transneuronally to first- and second-order structures connected with the olfactory bulb.[11] Certain neuronal populations are then sequentially infected by neuron-to-neuron propagation, affecting areas of the CNS such as the midbrain. Remarkably, these animal models have shown that the virus induces minimal cellular infiltration around infected neurons[11,15,17] and is not detected in the CSF, as in our case.[17]

We recently reported 3 other patients with COVID-19 who subsequently developed hyposmia, somnolence, and generalized myoclonus.[18] We hypothesized that SARS–CoV-2 can sequentially affect certain neuronal populations from the olfactory bulb to the diencephalon, eventually reaching the brainstem.[18]

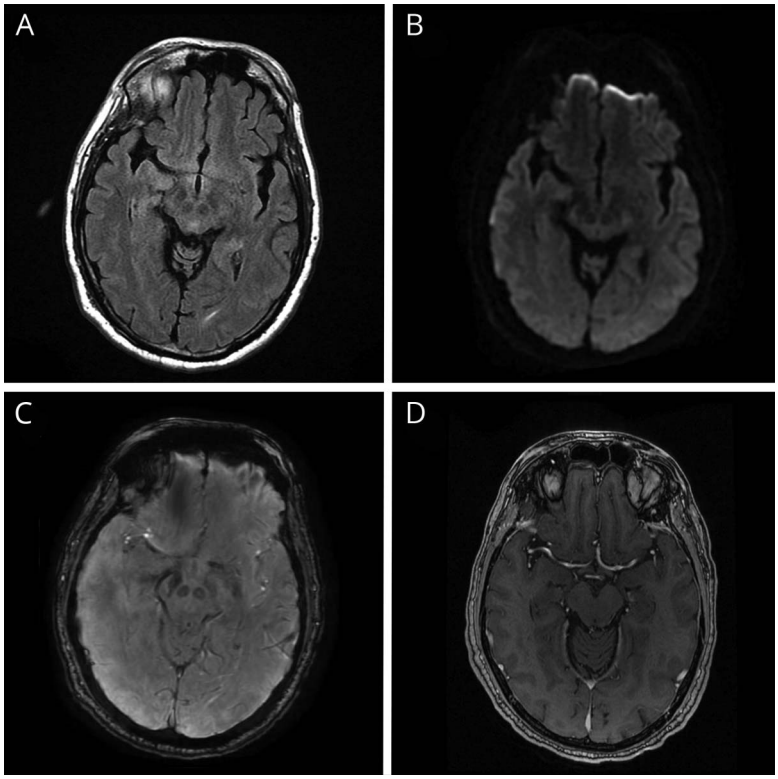
Because no good alternative explanation exists for the occurrence of an asymmetric hypokinetic-rigid syndrome, and all the signs and symptoms of the patient cannot be attributed to any known neurologic disease, we believe that this case study suggests that the CNS is affected by SARS–CoV-2. In this case, we assume that normal MRI findings with no contrast enhancement and a lack of pleocytosis in the CSF cannot rule out neuron infection. We hypothesized this on the basis of the aforementioned experimental animal studies, which showed no histologic lesions or encephalitis.[11,15,17] We have no explanation for the high CSF protein levels because neither the blood-brain barrier dysfunction nor oligoclonal bands were detected in the CSF. Additional studies quantifying brain-derived proteins in the CSF (such as neurofilaments, α-synuclein, or tau protein), markers for neuronal damage (i.e., neuron-specific enolase), and markers for microglia activity (i.e., neopterin) are needed.

Figure 2 Brain MRI (basal ganglia level)



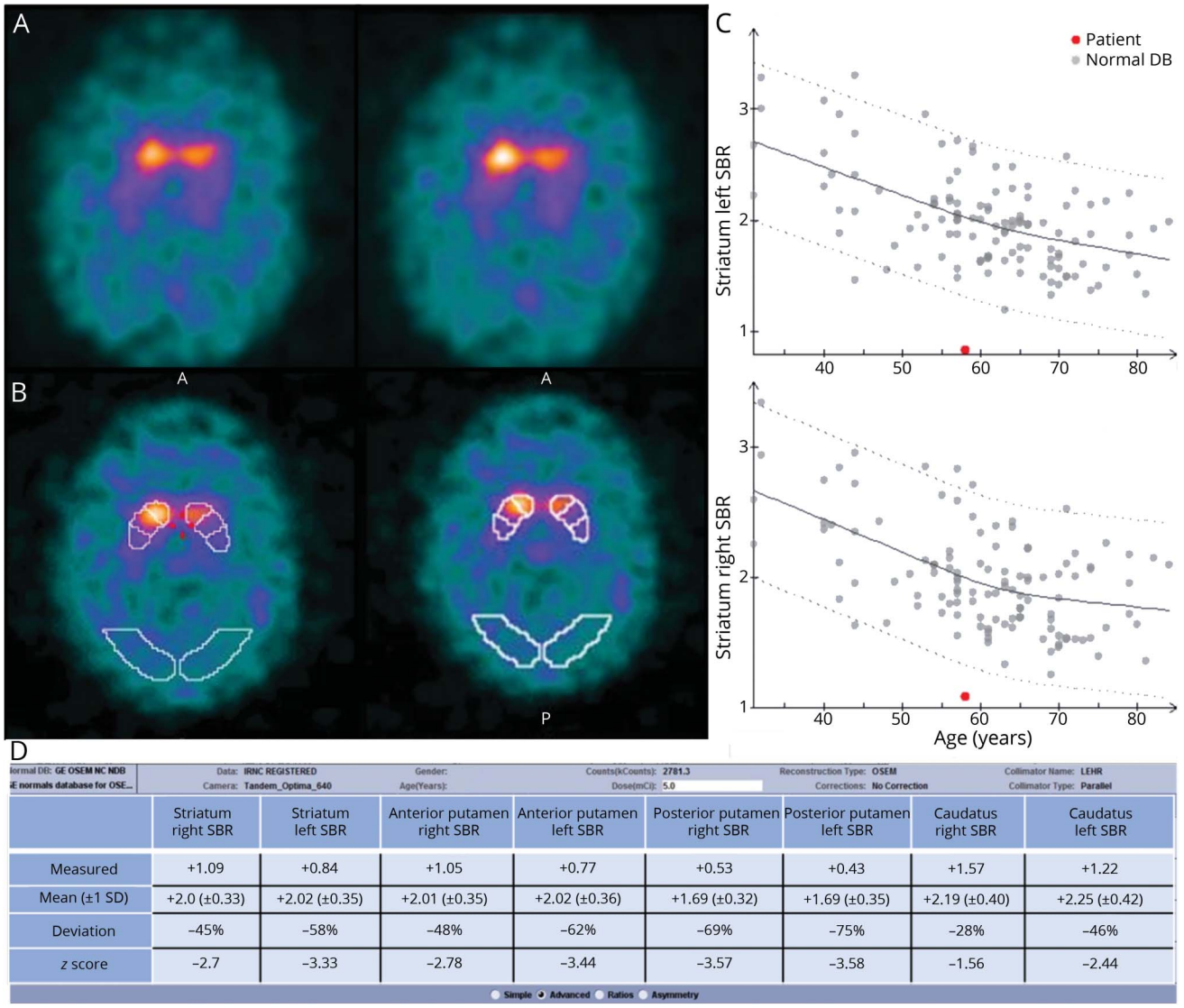
(A) Axial fluid-attenuated inversion recovery image shows no abnormal signal within brain parenchyma. (B) Axial diffusion-weighted imaging sequence shows no evidence of restricted diffusion. (C) Axial susceptibility-weighted imaging shows no microbleeds and no signs of brain iron deposition. (D) Axial gadolinium-enhanced T1-weighted image does not show abnormal enhancement.

Figure 3 Brain MRI (midbrain level)



(A) Axial fluid-attenuated inversion recovery image shows no abnormal signal within brain parenchyma. (B) Axial diffusion-weighted imaging sequence shows no evidence of restricted diffusion. (C) Axial susceptibility-weighted imaging shows no microbleeds and no signs of brain iron deposition. (D) Axial gadolinium-enhanced T1-weighted image does not show abnormal enhancement.

Figure 4 DaT-SPECT



	Striatum right SBR	Striatum left SBR	Anterior putamen right SBR	Anterior putamen left SBR	Posterior putamen right SBR	Posterior putamen left SBR	Caudatus right SBR	Caudatus left SBR
Measured	+1.09	+0.84	+1.05	+0.77	+0.53	+0.43	+1.57	+1.22
Mean (±1 SD)	+2.0 (±0.33)	+2.02 (±0.35)	+2.01 (±0.35)	+2.02 (±0.36)	+1.69 (±0.32)	+1.69 (±0.35)	+2.19 (±0.40)	+2.25 (±0.42)
Deviation	−45%	−58%	−48%	−62%	−69%	−75%	−28%	−46%
z score	−2.7	−3.33	−2.78	−3.44	−3.57	−3.58	−1.56	−2.44

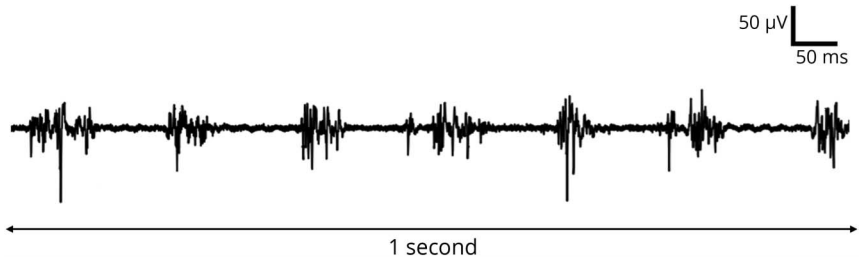
(A) Dopamine transporter (DaT)-SPECT shows a bilaterally reduced nigrostriatal absorption, affecting both putamina, yet asymmetrically, with greater deterioration of the left one. (B) DaTQUANT processing shows a separately delineated voxel of interest (VOIs) to fit the striatum. Reference VOIs are established in the bilateral occipital lobes. (C) Gray dots represent the average value from the normal database (DB) cases; dashed lines represent the 95% confidence interval (2 SDs from the mean); and a red dot represents our case in the both right and left striatal regions of the brain. (D)Striatal binding ratio (SBR) results and age-corrected *z* score for the left and right striatum are shown in the table. The SBR value is an accurate kinetic parameter that serves as a quantitative evaluation index of specific DAT binding.

The patient experienced a striking but incomplete symptomatic improvement after 14 days without any specific treatment. Some animal models have proposed cellular dysfunction of nigrostriatal neurons resulting from a viral infection.[11] Whether this mechanism,[11] a cytolytic effect on neurons,[15,17] or both processes are involved in this clinical case is a question that cannot be answered at the present time. However, clinical evolution and repeated DaT-SPECT tests will, we hope, shed some light on this issue.

Parainfectious or immune mechanisms affecting the neural function of different midbrain structures might also be considered after COVID-19, and on the basis of the current knowledge, this theory cannot be discarded.

The current report raises concern about the possible short-term effects of SARS–CoV-2 on the nervous system. Several studies have shown that viruses can activate the innate CNS immune system, causing long-lasting responses in the brain that may persist for years and contribute to protein aggregation disorders and neurodegeneration.[11,19] Accordingly, long-term effects may be detected in the future.

Figure 5 Electromyography



Needle EMG of right biceps brachii at rest (1-second epoch) shows a tremor with a frequency of 7 Hz.

This case study provides clinical and functional neuroimaging evidence to support that SARS–CoV-2 could gain access to the CNS, affecting midbrain structures and causing neurologic signs and symptoms. Overall, this is a single case report, and more observations are needed to determine whether the CNS is affected by SARS–CoV-2.

Acknowledgment

The authors acknowledge the patient and his family for understanding the hardships and uncertainties that such an extraordinary clinical picture has implied and for their collaboration in the hope of their case helping other patients. They acknowledge all health workers, patients, and everybody else worldwide who, when facing this once-in-a-lifetime challenge, have taught the value of generosity, determination, and hope in the midst of this pandemic. They also acknowledge Dr. J. Ruiz, whose enthusiasm for and wisdom about neurology have always been a model.

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Disclosure

A. Méndez-Guerrero, M.I. Laespada-García, A. Gómez-Grande, M. Ruiz-Ortiz, V.A. Blanco-Palmero, J.F. Azcarate-Diaz, P. Rábano-Suárez, E. Álvarez-Torres, C.P. de Fuenmayor-Fernández de la Hoz, D. Vega Pérez, R. Rodríguez-Montalbán, A. Pérez-Rivilla, J. Sayas Catalán, A. Ramos-González, J. González de la Aleja report no relevant disclosures. Go to Neurology.org/N for full disclosures.

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Appendix Authors

Name	Location	Contribution
Antonio Méndez-Guerrero, MD	Department of Neurology, University Hospital "12 de Octubre," Madrid, Spain	Conception, organization, and execution of the research project; writing of the first draft; and the review and critique of the manuscript
María Isabel Laespada-García, MD	Department of Neurology, University Hospital "12 de Octubre," Madrid, Spain	Conception, organization, and execution of the research project; writing of the first draft; and review and critique of the manuscript
Adolfo Gómez-Grande, MD	Department of Nuclear Medicine, University Hospital "12 de Octubre," Madrid, Spain	Nuclear medicine images analysis and the review and critique of the manuscript
Mariano Ruiz-Ortiz, MD	Department of Neurology, University Hospital "12 de Octubre," Madrid, Spain	Conception, organization, and execution of the research project; writing of the first draft; and review and critique of the manuscript
Víctor Antonio Blanco-Palmero, MD	Department of Neurology, University Hospital "12 de Octubre," Madrid, Spain	Conception, organization, and execution of the research project; writing of the first draft; and review and critique of the manuscript
Francisco Javier Azcarate-Diaz, MD	Department of Neurology, University Hospital "12 de Octubre," Madrid, Spain	Conception and organization of the research project; video editing; review and critique of the manuscript
Pablo Rábano-Suárez, MD	Department of Neurology, University Hospital "12 de Octubre," Madrid, Spain	Conception, organization, and execution of the research project; writing of the first draft; and review and critique of the manuscript
Eva Álvarez-Torres, MD, PhD	Department of Anesthesiology, University Hospital "12 de Octubre," Madrid, Spain	Organization of the research project; review and critique of the manuscript
Carlos Pablo de Fuenmayor-Fernández de la Hoz, MD	Department of Neurology, University Hospital "12 de Octubre," Madrid, Spain	Conception and organization of the research project; electrophysiologic study; and review and critique of the manuscript

Continued

Appendix *(continued)*

Name	Location	Contribution
Diana Vega-Pérez, MD	Department of Nuclear Medicine, University Hospital "12 de Octubre," Madrid, Spain	Nuclear medicine images analysis; review and critique of the manuscript
Raquel Rodríguez-Montalbán, MD	Department Anesthesiology, University Hospital "12 de Octubre," Madrid, Spain	Organization of the research project; review and critique of the manuscript
Alfredo Pérez-Rivilla, MD	Department of Microbiology, University Hospital "12 de Octubre," Madrid, Spain	Organization of the research project; review and critique of the manuscript
Javier Sayas-Catalán, MD	Department of Pneumology, University Hospital "12 de Octubre," Madrid, Spain	Organization of the research project; review and critique of the manuscript
Ana Ramos-González, MD, PhD	Department of Neuroradiology, University Hospital "12 de Octubre," Madrid, Spain	Organization of the research project; review and critique of the manuscript
Jesús González de la Aleja, MD, PhD	Department of Neurology, University Hospital "12 de Octubre," Madrid, Spain	Conception, organization, and execution of the research project; writing of the manuscript first draft; and the review and critique of the manuscript

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