

Generalized myoclonus in COVID-19

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Abstract

Objective

To report 3 patients infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) who developed generalized myoclonus.

Methods

Patient data were obtained from medical records from the University Hospital “12 de Octubre,” Madrid, Spain.

Results

Three patients (2 men and 1 woman, aged 63–88 years) presented with mild hypersomnia and generalized myoclonus following the onset of the so-called inflammatory phase of coronavirus disease 2019 (COVID-19). All of them had presented previously with anosmia. Myoclonus was generalized with both positive and negative jerks, predominantly involving the facial, trapezius, sternocleidomastoid, and upper extremities muscles. These myoclonic jerks occurred spontaneously and were extremely sensitive to multisensory stimuli (auditive and tactile) or voluntary movements, with an exaggerated startle response. Other causes of myoclonus were ruled out, and none of the patients had undergone respiratory arrest or significant prolonged hypoxia. All of them improved, at least partially, with immunotherapy.

Conclusions

Our 3 cases highlight the occurrence of myoclonus during the COVID-19 pandemic as a post- or para-infectious immune-mediated disorder. However, we cannot rule out that SARS-CoV-2 may spread transneuronally to first- and second-order structures connected with the olfactory bulb. Further investigation is required to clarify the full clinical spectrum of neurologic symptoms and optimal treatment.

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Glossary

COVID-19 = coronavirus disease 2019; **rRT-PCR** = real-time reverse-transcriptase polymerase chain reaction; **SARS-CoV-2** = severe acute respiratory syndrome coronavirus 2.

The new severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has spread rapidly worldwide. The spectrum of coronavirus disease 2019 (COVID-19) ranges from asymptomatic infection to severe respiratory failure, with fever, cough, and fatigue being the most common clinical symptoms.¹ Other features, including neurologic manifestations (e.g., myalgia, headache, anosmia, and ageusia), have also been reported.^{1,2} Neurologists are now starting to see more severe neurologic manifestations associated with COVID-19,^{3–6} including acute cerebrovascular diseases, skeletal muscle injury, encephalopathy, prominent agitation and confusion, corticospinal tract signs, Guillain-Barré syndrome, Miller Fisher syndrome, and polyneuritis cranialis. The exact pathogenesis of COVID-19-induced neurologic manifestations remains largely unknown. Myoclonus has been reported in other viral infections,⁷ but not yet associated with SARS-CoV-2 infection.

We report 3 patients who developed generalized myoclonus as a predominant phenomenon during SARS-CoV-2 infection.

Methods

Data were obtained from patients admitted to University Hospital “12 de Octubre,” Madrid, Spain.

Standard protocol approvals, registrations, and patient consents

Written informed consent was obtained from the patients (consent for research).

Data availability

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

Results

Patient 1

A 63-year-old man was admitted to the emergency department because of a 7-day history of fever and anosmia. On day 8 after onset of symptoms, he noticed shortness of breath. One day later, he developed sudden onset of jerky movements in his face and limbs, which prevented him from eating and speaking properly. His medical history was remarkable for generalized anxiety disorder.

Except for a basal oxygen saturation of 93%, his vital signs were normal. A chest X-ray revealed bilateral diffuse patchy interstitial infiltrates consistent with COVID-19. The initial blood workup revealed elevated C-reactive protein, elevated

D-dimers, and lymphopenia. He was diagnosed with COVID-19. Nasopharyngeal swab test for SARS-CoV-2 by qualitative real-time reverse-transcriptase polymerase chain reaction (rRT-PCR) assay could not be performed due to its scarcity in Spain at that time.

By day 10 after onset of symptoms, myoclonus worsened, preventing the patient from moving, speaking, or swallowing. He was intubated and admitted to the intensive care unit owing to myoclonic storm. The neurologic examination at that time revealed mild somnolence with otherwise normal higher mental functions. He had no opsoclonus or other abnormalities in the cranial nerves. He showed generalized myoclonus, with both positive and negative jerks. They predominantly involved the facial, trapezius, sternocleidomastoid, and upper extremities muscles, worsened with voluntary movements, and augmented markedly with auditory and tactile stimuli. An exaggerated startle response was noticed (video 1). There was no motor or sensory deficit. Tone, deep tendon reflexes, and plantar responses were normal. Gait was greatly hindered by the movements.

Myoclonus only disappeared with deep propofol sedation but tended to reappear as it was withdrawn. Symptomatic treatment with levetiracetam, valproic acid, and clonazepam were initiated with scarce improvement. An extensive laboratory workup, including CSF analysis and cranial MRI, revealed no abnormalities. EEG showed no epileptiform discharges during myoclonus. The main findings of complementary tests are shown in the table.

We assumed the myoclonus to be an immune-mediated manifestation of the inflammatory phase of COVID-19. We started immunotherapy (methylprednisolone 1,000 mg/24 hours for 5 days), and the myoclonus seemed to improve slightly (video 1). The patient then could be extubated, without supplemental oxygen needs. Two days later, the myoclonus worsened again, and the patient had to be reintubated and started on plasmapheresis. The patient received a total of 5 daily plasma exchange treatments, showing clinical improvement after completion of therapy (video 1).

Patient 2

An 88-year-old woman was admitted to the emergency department because of a 2-day history of anosmia, fever, and shortness of breath. Chest-X-ray revealed bilateral pneumonia. Her medical history was remarkable for arterial hypertension, hypothyroidism, a nonfunctioning pituitary adenoma, and mild cognitive decline with no history of abnormal movement

Table Complementary tests

	Patient 1	Patient 2	Patient 3
Basic laboratory findings on arrival			
White cell count per mm ³	13,400	6,500	18,300
Neutrophils	11,700	5,200	15,200
Lymphocytes	500	900	500
Platelet count per mm ³	483,000	243,000	401,000
Hemoglobin, g/L	12.4	13.2	15.5
Transaminases	Normal	Normal	Normal
Lactate dehydrogenase, U/L	223	320	431
Creatinine kinase, U/L	79	—	164
C-reactive protein, mg/L	9.17	1.3	6.2
Serum ferritin, ng/mL	—	127	1,850
Procalcitonin, ng/mL	0.05		0.261
Coagulation test abnormalities	Fibrinogen 818 g/L	—	Prothrombin time 15.3 seconds, fibrinogen 677 g/L
D-dimer, mg/L	4,784	867	18,239
Blood ions (Na, Cl, K, Ca, Mg, P)	Normal	Normal	Normal
Creatinine, mg/dL	0.81	1.12	0.82
Urea and ammonia	Normal	Normal	Normal
Thyroid function	Normal	Normal	Normal
Serologies	HIV and syphilis negative	HBV past infection, HIV, HCV, and syphilis negative	HIV and syphilis negative
CSF analyses			
Basic biochemistry and white cell count in CSF	Normal	—	
Microbiological studies	Negative	—	
Autoimmune disorders screening			
Non-organospecific autoimmune disorders ^a	Negative	Negative	Negative
Onconeural and antineuronal surface antibodies (serum) ^b	Negative	—	Negative

Continued

Table Complementary tests (continued)

	Patient 1	Patient 2	Patient 3
Onconeural and antineuronal surface antibodies (CSF)^b	Negative	—	—
Other	Negative for anti-GAD 65 and antithyroid antibodies (antithyroid peroxidase antibodies, antithyroglobulin antibodies, and anti-TSH receptor antibodies)	—	Negative for anti-GAD 65 and anti-glomerular basement membrane antibodies
Neuroimaging			
Cranial CT scan	Normal	Normal	Normal
Brain MRI scan (with and without gadolinium)	Normal	—	Normal
Chest X-ray or chest CT scan	Bilateral peripheral infiltrates	Bilateral peripheral infiltrates	Chest CT scan showed bilateral peripheral ground-glass opacifications involving lower lobes, with an area of consolidation in right lung
Other	—	—	Body CT scan without additional relevant findings
EEG	Mild diffuse slowing (reactive) without epileptic activity	Mild diffuse slowing without epileptic activity	Mild diffuse slowing (reactive) without epileptic activity
Medications			
Previous chronic medications	Bromazepam	Acetylsalicylic acid, atenolol, levothyroxine, valsartan	None
Additional medications during admission	Acetaminophen, azithromycin, ceftriaxone, cisatracurium, clonazepam, dexmedetomidine, enoxaparin, hydroxychloroquine, levetiracetam, lopinavir/ritonavir, methylprednisolone, midazolam, omeprazole, propofol, valproic acid	Acetaminophen, azithromycin, enoxaparin, methylprednisolone, omeprazole	Acetaminophen, azithromycin, bisoprolol, clonazepam, enoxaparin, hydroxychloroquine, levetiracetam, omeprazole

Abbreviations: HBV = hepatitis B virus; HCV = hepatitis C virus.

^a Antibodies included: 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-AMPA1/R2, anti-LGI-1, anti-DDPX, anti-GABA_BR; onconeural antibodies: anti-GAD65, anti-SOX1, anti-Ma-1, anti-Ma-2, anti-amphiphysin, anti-CV2, anti-Ri, anti-Yo, anti-Hu.

disorders. The patient's nasopharyngeal swab test for SARS-CoV-2 by qualitative rRT-PCR assay was positive.

By the third week since the onset of symptoms, the patient started having mild hypersomnia and similar jerking movements to patient 1, but milder. Brain CT, EEG, and extensive laboratory workup were unrevealing (table). The myoclonus disappeared with methylprednisolone pulses (250 mg/24 hours for 3 days).

Patient 3

A 76-year-old man with no medical comorbidities had fever, malaise, cough, anosmia, ageusia, and myalgia for 10 days. On day 11 from the onset of symptoms, he developed jerky movements in his face and limbs, mild somnolence, and dyspnea. Myoclonic jerks were milder, but similar to those in patient 1. He was diagnosed with SARS-CoV-2 pneumonia based on the clinical features, blood analysis, radiologic

picture, and epidemiologic context. Nasopharyngeal swab test for SARS-CoV-2 by rRT-PCR assay was not performed due to its scarcity in Spain at that time. Brain MRI and EEG were unrevealing. The patient experienced no benefit from clonazepam and levetiracetam. He received methylprednisolone pulses (250 mg/24 hours for 3 days) to treat COVID-19 pneumonia. Two weeks later, the patient started experiencing a spontaneous progressive improvement.

Other patients

We have encountered other patients with COVID-19 who also presented with myoclonus. Regarding these other cases, myoclonus could also be explained by drugs, metabolic disturbances, or severe hypoxia. However, as a preliminary impression, there seems to be an increasing, unexpected amount of severe myoclonus among some of the hundreds of patients admitted to our hospital with COVID-19 infection.

Discussion

To our knowledge, these are the first reported cases of generalized myoclonus in COVID-19. After a thorough study, no other potential causes for this phenomenon were identified. No serious metabolic disturbances were registered, and none of the patients underwent severe hypoxia. No causative drugs were administered, and we did not find autoantibodies that could account for a known immune-mediated disorder. CSF analysis was performed in patient 1 and revealed no relevant abnormalities, and neuroimaging studies were normal in all of the patients.

Jerking movements of our patients could be attributable to brainstem myoclonus, a type of myoclonus originating from the lower brainstem, which is characterized by initial muscle activation in muscles innervated in the lower brainstem followed by a sequence of both higher brainstem innervated muscles and muscles innervated further down the spinal cord.⁸ Worsening of myoclonus with movements, tactile stimuli, and specially the exaggerated startle response also support this hypothesis.⁸ EEG studies performed ruled out an epileptic myoclonus, but further neurophysiologic (i.e., EMG) tests could not be performed due to logistic limitations in the setting of the current pandemic.

Regarding myoclonus pathophysiology in COVID-19, we raise 2 possibilities. First, a post- or para-infectious immune-mediated mechanism is possible. Consistent with this hypothesis, postinfectious myoclonus presenting shortly after the start of infections caused by other viruses (occasionally in the form of opsoclonus-myoclonus,⁹ but also as isolated myoclonus)¹⁰ has been reported. Furthermore, our patients started presenting myoclonus following the onset of the so-called inflammatory phase of COVID-19.¹¹ Second, several reports have proved the neuroinvasive potential of SARS-CoV in humans.^{12–15} Experimental studies have demonstrated that SARS-CoV,¹⁶ as other respiratory viruses, such as H1N1 influenza virus,^{17,18} when inoculated intranasally, could spread transneuronally to first- and second-order structures connected with the olfactory bulb. Certain neuronal populations with sleep–wake regulatory functions in the hypothalamus as well as noradrenergic neurons in the locus coeruleus and serotonergic neurons in the dorsal raphe were infected in those models in the absence of encephalitis.^{16–18} As our 3 patients consecutively presented hyposmia, hypersomnia, and generalized myoclonus, we cautiously hypothesize that SARS-CoV-2 could affect these structures (olfactory bulb and brainstem) sequentially. Furthermore, normal brain MRI and lack of pleocytosis in the CSF cannot rule out this mechanism, because no histologic lesions were observed surrounding infected neurons in the aforementioned studies.^{16–18}

All our patients received a short cycle of high-dose methylprednisolone and one of them received plasma exchange sessions. As not only neuronal death has been described in animal models,^{16,17} but also noncytolytic effects on neurons,¹⁸ whether clinical improvement is related to the treatment

administered or is related to a natural and self-limited evolution should be addressed in future studies.

We recognize that the main limitations of each of the cases was the absence of EMG and in 2 of them the absence of nasopharyngeal swab test for SARS-CoV-2 by rRT-PCR assay. The reason for this was the extreme circumstances in our hospitals at the peak of this pandemic.

We describe 3 patients with COVID-19 with generalized myoclonus who had good outcomes. The acute onset of myoclonus in the context of the inflammatory response to SARS-CoV-2 infection, together with the similarities with other viral-triggered myoclonus, and the improvement after immunotherapy leads us to hypothesize that this could have a post- or para-infectious immune-mediated mechanism. However, we cannot rule out that SARS-CoV-2 may spread transneuronally to first- and second-order structures connected with the olfactory bulb, which would be supported by the sequential appearance of hyposmia, hypersomnia, and generalized myoclonus. Further investigation is required to clarify the full clinical spectrum of neurologic symptoms and its optimal treatment.

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Disclosure

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Appendix (continued)

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Appendix (continued)

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