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Generalized myoclonus in COVID-19

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ABSTRACT

Objective: To report three 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 (two men, and one woman, aged 63 to 88) 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 had a stereotypical pattern, being both positive and negative, generalized, with a predominant involvement of nasopharyngeal, facial, and upper limbs areas. These jerky movements occurred spontaneously and were extremely sensitive to multisensory stimuli (auditive and tactile) or voluntary movement, with an exaggerated startle response. Other causes of myoclonus were ruled-out, and none of them had undergone respiratory arrest or significant prolonged hypoxia. All of them improved, at least partially, with immunotherapy.

Conclusions: Our three cases highlight the occurrence of myoclonus during the COVID-19 pandemic as a postinfectious / 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 neurological symptoms and its optimal treatment.
The new severe acute respiratory syndrome coronavirus (SARS-CoV-2) has rapidly spread worldwide. The spectrum of the coronavirus disease 2019 (COVID-19) ranges from asymptomatic infection to severe respiratory failure, being fever, cough, and fatigue the most common clinical symptoms. Other features, such as neurological manifestations (e.g., myalgia, headache, anosmia and ageusia) have also been reported. However, neurologists are now starting to see more severe neurological manifestations associated with COVID-19, including acute cerebrovascular diseases, skeletal muscle injury, encephalopathy, prominent agitation and confusion, corticospinal tract signs, Guillain-Barré syndrome, Miller Fisher syndrome and polyneuritis cranialis. However, the exact pathogenesis of COVID-19-induced neurological manifestations largely remains unknown. Myoclonus has been reported in other viral infections, but not yet associated with SARS-CoV-2 infection.

We herein report three 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 three patients participating in the study (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 room 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 suddenly started with jerky movements in his face and limbs, that prevented him to eat and even speak properly. His past 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 infection. The initial blood work-up revealed elevated C-reactive protein, elevated D-dimers, and lymphopenia. He was diagnosed with COVID-19 infection due to the clinical-radiological picture. The patient’s 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 moment.

By the day 10 after onset of symptoms, myoclonus worsened preventing the patient to move, speak, or swallow for which he was intubated and admitted to the intensive care unit due to a "myclonic storm". The neurological examination, at that moment, revealed mild somnolence with otherwise normal higher mental functions. He had no opsoclonus or other abnormalities in the cranial nerves. He showed asynchronous, generalized myoclonus, with both positive and negative jerks. They predominantly involved the craniofacial and superior limbs region, worsened with voluntary movements, and augmented markedly with auditory and tactile stimuli. An exaggerated startle response was noticed (video). There was no motor nor sensory deficit. The tone, deep tendon reflexes and plantar responses were normal. The 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 work-up, including cerebrospinal analysis and a cranial magnetic resonance imaging (MRI) revealed no abnormalities. Electroencephalography (EEG) showed no epileptiform discharges during myoclonus. The main findings of complementary tests are shown in table.

We assumed the myoclonus to be a postinfectious / immune-mediated manifestation of the so-called “inflammatory” phase of COVID-19. We started immunotherapy (methylprednisolone 1000 mg/24 hours for five days), and the myoclonus seemed to improve slightly. He could then be extubated, without supplemental oxygen needs. Nevertheless, two days after, myoclonus worsened again, and the patient had to be re-intubated, and started on plasmapheresis. The patient received a total of five daily plasma exchanges treatments, showing clinical improvement after completion of therapy.

**Patient 2.** A 88-year-old woman was admitted to the emergency room because of a 2-day history of anosmia, fever, and shortness of breath. Chest-X-ray revealed a bilateral pneumonia. Her past medical history was remarkable for arterial hypertension, hypothyroidism, a non-functioning pituitary adenoma, and mild cognitive decline with no history of abnormal movements 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, she started having mild hypersomnia and similar jerking movements to patient 1, but milder. A brain computerized tomography, EEG, and extensive laboratory work-up were unrevealing (see table). Finally, 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, anosmia, ageusia and myalgia for 10 days. At day 11, since the onset of symptoms, he developed facial and limb jerking, mild somnolence, and dyspnea. Jerking movements were milder, but like patient 1. He was diagnosed with SARS-CoV2 pneumonia, based on the clinical, blood
analysis, radiological picture, and considering epidemiological context. The patient’s nasopharyngeal swab test for SARS-CoV-2 by rRT-PCR assay was not performed due to its scarcity in Spain at that moment. Brain MRI and EEG were unrevealing. He experienced no benefit with clonazepam and levetiracetam altogether. In addition, 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 simply by severe hypoxia. However, and 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, which could account for a known immune-mediated disorder. Cerebrospinal fluid analysis was performed in patient 1 without relevant abnormalities, and neuroimaging studies were normal in all of them.

Jerking movements of our patients could be attributable to the so called brainstem myoclonus, a type of myoclonus originating from the lower brainstem, which typically presents as multifocal, with marked involvement of proximal rather than distal limb
muscles. Worsening of myoclonus with movement, tactile stimuli and specially the exaggerated startle response also support this hypothesis. EEG studies performed ruled out an epileptic myoclonus, but further neurophysiologic (i.e., electromyography) tests could not be performed due to logistic limitations in the setting of the current pandemic.

Regarding myoclonus pathophysiology in COVID-19 infection, we raise two possibilities. First, a postinfectious / immune-mediated origin. Consistently with our observations, postinfectious myoclonus presenting shortly after the start of infections caused by other viruses (occasionally in the form of opsoclonus-myoclonus, but also as isolated myoclonus), have also been ascribed to a reticular origin. Our patients satisfied the criteria, proposed by Bhatia et al., for postinfectious etiology. Furthermore, our patients started presenting myoclonus several days after onset of respiratory symptoms, with systemic markers indicative of the so-called cytokine release syndrome. Second, several reports have proved the neuroinvasive potential of SARS-CoV in humans. Experimental studies have demonstrated that SARS-CoV, as other respiratory viruses, such as H1N1 influenza virus, 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. As our three 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 cerebrospinal fluid cannot rule out this mechanism, because no histological lesions were observed surrounding infected neurons in the aforementioned studies.

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

In conclusion, we describe three 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 postinfectious / immune-mediated origin. 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 neurological symptoms and its optimal treatment.
### APPENDIX. AUTHORS

<table>
<thead>
<tr>
<th>Name</th>
<th>Location</th>
<th>Contribution</th>
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<tbody>
<tr>
<td>Pablo Rábano-Suárez, MD</td>
<td>Department of Neurology, University Hospital “12 de Octubre”, Madrid, Spain</td>
<td>Conception, organization and execution of the research project; writing of the first draft and the review and critique of the manuscript</td>
</tr>
<tr>
<td>Laura Bermejo-Guerrero, MD</td>
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<tr>
<td>Antonio Méndez-Guerrero, MD</td>
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<td>Conception, organization and execution of the research project; writing of the first draft and the review and critique of the manuscript</td>
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<tr>
<td>Javier Parra-Serrano, MD</td>
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<td>Conception and organization of the research project; review and critique of the manuscript</td>
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<td>Daniel Toledo-Alfocea, MD</td>
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<td>Conception and organization of the research project; review and critique of the manuscript</td>
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<tr>
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<td>Conception and organization of the research project; review and critique of the manuscript</td>
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<tr>
<td>Name</td>
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<tr>
<td>María Dolores Folgueira-Lópe, MD, PhD</td>
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<td>Conception and organization of the research project; review and critique of the manuscript</td>
</tr>
<tr>
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<td>Conception and organization of the research project; review and critique of the manuscript</td>
</tr>
<tr>
<td>Blanca Ayuso-García, MD</td>
<td>Department of Internal Medicine, University Hospital “12 de Octubre”, Madrid, Spain</td>
<td>Conception and organization of the research project; review and critique of the manuscript</td>
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<td>Jesús González de la Aleja, MD, PhD</td>
<td>Department of Neurology, University Hospital “12 de Octubre”, Madrid, Spain</td>
<td>Conception, organization and execution of the research project; writing of the first draft and the review and critique of the manuscript</td>
</tr>
<tr>
<td>Julián Benito-León, MD, PhD</td>
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<td>Conception, organization, and execution of the research project; writing of the manuscript first draft and the review and critique of the manuscript</td>
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REFERENCES


Table: Complementary tests.

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<td>C-reactive protein (mg/l)</td>
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<td>Procalcitonin (ng/ml)</td>
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<td><strong>Brain MRI scan (with and without)</strong></td>
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<td><strong>Chest-X-ray or chest CT scan</strong></td>
<td>Bilateral peripheral infiltrates</td>
<td>Bilateral peripheral infiltrates</td>
<td>Chest CT scan showing bilateral peripheral ground-glass opacifications involving lower lobes, with an area of consolidation in right lung</td>
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<td>Body CT scan without additional relevant findings</td>
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<td>Acetaminophen, azithromycin, enoxaparin, methylprednisolone, and omeprazol</td>
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HIV: human immunodeficiency virus; HBV: hepatitis B virus; HCV: hepatitis C virus.


** Encephalitis profile: anti-NMDAR, anti-CASPR2, anti-AMPAR1/R2, anti-LGI-1, anti-DDPX, anti-GABAbR; Onconeural antibodies: anti-GAD65, anti-SOX1, anti-Ma-1, anti-Ma-2, anti-amphiphysin, anti-CV2, anti-Ri, anti-Yo, anti-Hu
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