

Post-COVID-19 Myoclonus-Ataxia Syndrome Responsive to Intravenous Immunoglobulins

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During the coronavirus disease 2019 (COVID-19) pandemic, multisystemic syndromes related to viral infection have been described, with a range of neurological manifestations rapidly expanding.^{1,2} The commonly described and autoptically confirmed neurological disorders associated with COVID-19 include encephalitis, meningitis, anosmia/ageusia, Guillain-Barré syndrome, acute disseminated encephalomyelitis, and cerebrovascular events.³ Herein we report an emerging neurological manifestation associated with COVID-19, that is, myoclonus-ataxia syndrome. Unlike previous reported cases,⁴⁻⁷ the current patient was immunocompetent, developed the neurological complication with a clear postinfectious pattern, and significantly responded to intravenous immunoglobulin (IVIg).

Case Report

A 71-year-old man was referred to the emergency department (ED) because of subacute onset of involuntary jerky movements, unstable gait, and diffuse clumsiness at rest that worsened with movement 2 days after complete resolution of SARS-CoV-2 infection. Due to mild respiratory symptoms, he was treated at home with azithromycin only and no steroid was given because of type 2 diabetes in his past medical history. Apart from diabetes and hypertension (treated with metformin and ramipril, respectively), he did not have other comorbidities. Video 1 shows saccadic intrusions without opsoclonus, facial jerking, spontaneous generalized myoclonic jerks of the trunk and limbs (particularly involving the hands) at rest and clearly worsened both posturally and during voluntary movements, and cerebellar ataxia of the upper limbs and ataxic gait requiring bilateral assistance.

During hospitalization in the Neurology Department, he underwent extensive laboratory tests, including thyroid functioning, celiac disease serology, and testing for antibodies against

neuronal surface antigens and onconeural antibodies both in serum and cerebrospinal fluid (CSF); electroencephalogram (EEG); neuropsychological assessment; brain magnetic resonance imaging (MRI) with gadolinium; brain and total body ¹⁸fluorodeoxyglucose positron emission tomography; and CSF analysis. All of these investigations revealed no abnormality, whereas electro-neurography showed signs of diffuse mild axonal damage. Polymerase chain reaction for SARS-CoV-2 in the CSF was negative, and oligoclonal bands were not detected. Serology indicated a past infection for SARS-CoV-2. At 1 month after the onset of neurological manifestations, he did not show spontaneous recovery or any benefit from symptomatic treatment with clonazepam. Therefore, IVIg were given (0.4 g/kg per day for 5 days), which produced a prompt and remarkable improvement. A neurological examination repeated 17 days after IVIg administration (Video 2) showed a significant improvement of ataxia (he was able to walk unassisted) and myoclonus (which was no more evident); no facial jerking was present. Any further treatment was not needed.

Discussion

We report a case of post-COVID-19 myoclonus-ataxia syndrome in a fully immunocompetent patient successfully treated with IVIg. Extensive diagnostic workup excluded other causes. Although COVID-19-associated myoclonus has been described,⁸ the present case demonstrated not only a generalized myoclonus but also a clear cerebellar involvement. Moreover, unlike the previously published cases,⁴⁻⁷ our patient had a mild pulmonary disease and did not have any feature of encephalopathy. Also, differently from a previous HIV-positive case on anti-retroviral therapy,⁹ our patient was immunocompetent, and his symptoms did not develop during the pulmonary infection but when he became seronegative for COVID-19.

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Keywords: SARS-CoV-2 infection, post-COVID-19, myoclonus, ataxia, immunoglobulin.

Received 28 October 2021; revised 27 January 2022; accepted 29 January 2022.

Published online 00 Month 2022 in Wiley Online Library (wileyonlinelibrary.com). DOI: 10.1002/mdc3.13534



Video 1. Saccadic intrusions without opsoclonus, facial jerking, spontaneous generalized myoclonic jerks of the trunk and limbs (particularly involving the hands) at rest and clearly worsened both posturally and during voluntary movements, and cerebellar ataxia of the upper limbs and ataxic gait requiring bilateral assistance are shown.

Video content can be viewed at <https://onlinelibrary.wiley.com/doi/10.1002/mdc3.13534>



Video 2. Neurological examination 17 days after IVIg administration showed a significant improvement of ataxia (he was able to walk unassisted) and myoclonus (which was no more evident); no facial jerking was present.

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The anatomical substrate of myoclonus is likely to be subcortical, as he predominantly had generalized myoclonus, mostly synchronous and most prominent in the distal upper limbs and trunk, with normal brain MRI and EEG. He also had truncal ataxia, which might be related to a vermian involvement, although the impairment of gait could be also attributable to truncal and proximal lower limb myoclonus. This is not surprising, as the neurological spectrum of COVID-19 is constantly expanding, and a recent case of opsoclonus myoclonus–ataxia syndrome has been published.¹⁰

In the present patient, the subacute onset of neurological symptoms after the clinical resolution and negative serology of COVID-19 suggests a postinfectious immune-mediated etiology. Alternative pathophysiology might be a direct trans-neural spread of the virus to the central nervous system

through the olfactory tract, although this seems to be unlikely given the timing of the symptomatology and the negative results from all the exams performed. Other mechanisms include hypoxia or iatrogenic cause,⁷ which however can be ruled out because of his mild respiratory symptoms and the lack of any causable drug taken.

Finally, our patient did not recover spontaneously but, rather, immunotherapy was needed, which induced a rapid and significant clinical improvement. Although he did not need any other treatment after IVIg, however, it cannot be excluded that the favorable outcome might have been coincidental or that IVIg has just accelerated his recovery. In this context, although all the reported cases improved following different treatments, the speed and degree of recovery was variable. Indeed, the effect of medications is heterogeneous, with some patients who responded very well to symptomatic therapy (such as the antimyoclonic drugs) and others who had to escalate to plasma exchange due to the lack of any response to antimyoclonic medications and steroids.^{7,8}

In conclusion, as COVID-19 is now viewed as a multisystemic disease with pleiomorphic manifestations, increased awareness among neurologists, ED physicians, intensivists, and even general practitioners about the neurological features is needed. SARS-CoV-2 infection should be considered among the possible causes of myoclonus–ataxia syndrome also in immunocompetent patients with mild COVID-19 manifestations. IVIg can be a valid treatment choice in cases of myoclonus–ataxia without spontaneous recovery or in nonresponders to symptomatic drugs.

Author Roles

(1) Research Project: A. Conception, B. Organization, C. Execution; (2) Manuscript: A. Writing of the First Draft, B. Review and Critique.

M.G.: 1A, 1C, 2B

A.B.: 1B, 1C, 2B

G.L.: 1A, 1B, 2A

Disclosures

Ethical Compliance Statement: The study was performed in accordance with the Declaration of Helsinki of 1964 and its later amendments. Written informed consent was obtained from the patient. Ethical approval was waived due to the nature of the report itself, which was based on clinical examinations and within the diagnostic workup expected for this patient. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this work is consistent with those guidelines.

Funding Sources and Conflicts of Interest: The authors declare that there are no funding sources or conflicts of interest relevant to this work.

Financial Disclosures for Previous 12 Months: The authors declare that there are no additional disclosures to report. ■

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The image shows a presentation slide for the 'MDS Video Challenge'. The slide is titled '3 Cases' and is divided into two sections. The first section, for Iran, features the Iranian flag and lists '2 from Iran' submitted by 'Maziar Emamikhah' from the 'Iran University of Medical Sciences, Tehran'. The second section, for Italy, features the Italian flag and lists '1 from Italy' submitted by 'Giuseppe Lanza' from the 'University of Genoa-IRCCS Ospedale Policlinico, San Martino'. A small inset video shows a man in a suit speaking. The slide also includes the 'MDS VIDEO CHALLENGE' logo and the 'MDS Virtual Congress 2021' logo, which specifies the dates 'SEPTEMBER 17-22, 2021' and the website 'www.mdscongress.org'.

Video 3. Full video from the 2021 Video Challenge discussion of this case.
Video content can be viewed at <https://onlinelibrary.wiley.com/doi/10.1002/mdc3.13534>