

LETTER TO THE EDITOR**To THE EDITOR****Ataxia-Myoclonus Syndrome in Patients with SARS-CoV-2 Infection**

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The most common manifestations of SARS-CoV-2 infection include cough, fever, dyspnoea, musculoskeletal (myalgia, joint pain, fatigue) and gastrointestinal features as well as anosmia/dysgeusia. Moreover, a plethora of neurological symptoms have been described either directly or indirectly caused by COVID-19, including encephalopathies, para/post-infectious CNS syndromes, cerebrovascular diseases (ischaemic and haemorrhagic) and infection-triggered autoimmune peripheral nervous system disorders, such as Guillain-Barré syndrome.¹ In the movement disorder spectrum, myoclonus has been observed as an isolated occurrence² or as included in opsoclonus-myoclonus-ataxia syndrome.³

A 50-year-old man was admitted to our Internal Medicine Unit complaining of severe fatigue while walking and unsteady gait, followed by new onset of jerks during intentional movements, after asymptomatic SARS-CoV-2 infection (Case 1). Indeed, a positive nasopharyngeal swab to detect COVID-19 was performed 10 days before, since his wife was diagnosed with SARS-CoV2 infection firstly. His past medical history was unremarkable. Vital signs were normal, except for a sinus tachycardia. Arterial blood gas analysis in ambient air excluded respiratory failure.

Physical general examination revealed bilateral basal lung crackles only. Neurological examination showed action-induced myoclonus involving face, upper limbs and trunk (Video 1, segment 1). At eye movement examination, pursuits were parasitised by horizontal saccadic intrusions and no obvious opsoclonus (Video 1, segment 2). Prominent titubation, unbalance while standing upright and gait ataxia, was noted (Video 1, segment 3). Sensory abnormalities were absent. The previously known stutter did not exacerbate recently.

Blood tests showed mild leukocytosis and thrombocytosis, increased LDH and CK values with slightly increased C-reactive protein (CRP). Troponin, coagulation tests, renal and hepatic function tests and electrolytes were unremarkable. Vitamin B12 or folic acid deficiency was excluded. A chest X-ray evidenced bilateral lung reticular interstitial opacification.

Other (metabolic, autoimmune, paraneoplastic, and infective) causes of myoclonus were excluded. For the sake of diagnosis, brain MRI was scheduled but interrupted because of patient's claustrophobia. Lumbar puncture, electroencephalogram (EEG) and electromyography (EMG) were not performed due to logistic limitations related to the pandemic and the patient's clinical improvement.

Thus, based on similar clinical pictures reported in the literature,⁴ a SARS-CoV-2-related acute cerebellar ataxia and myoclonus (ACAM) was diagnosed. Therefore, the patient underwent high doses of intravenous glucocorticoid infusion (methylprednisolone 250 mg/day) for 3 days and then orally

with progressive resolution of neurological symptoms within a week (Video 1, segment 4).

An 80-year-old man was admitted for an about 10-day history of mild dyspnoea, fever and cough followed by acute onset of unsteady gait and generalised involuntary jerks in the last 2 days (Case 2). Acute COVID-19 interstitial pneumonia was diagnosed since nasopharyngeal swab was positive and high-resolution CT chest scan showed bilateral ground-glass opacities compatible with interstitial lung disease. So, the patient was hospitalised in the COVID Unit. His past medical history included hypertension, hypercholesterolaemia, a previous myocardial infarction in 2011 treated with percutaneous coronary intervention, severe aortic valve stenosis treated with aortic valve replacement with a mechanical valve prosthesis and a mild sensorimotor axonal-demyelinating polyneuropathy. At admission, he required oxygen supplementation (Venturi Mask 31%O₂) because of low oxygen saturation (SpO₂ 88% in ambient air). Neurological examination showed the presence of generalised action-induced myoclonus together with ataxia in the upper and lower extremities (Video 2) and ataxic speech. At eye movement examination, pursuits were parasitised by horizontal saccadic intrusions. The patient was not able to walk or to keep the standing position due to the severe trunk and gait ataxia. There were no obvious sensory or motor signs. Blood tests revealed leukocytosis and mild thrombocytopenia, with slight CRP increment. Coagulation tests, renal and hepatic function and electrolytes were normal. Vitamin B12 or folic acid deficiency was excluded as well. Brain CT was unremarkable. The brain MRI scan was immediately interrupted because of the incidentally finding of an unknown metallic object close to the heart. EMG disclosed no significant changes compared to the previous test. Lumbar puncture and EEG were not performed due to logistic limitations related to the pandemic. High doses of glucocorticoid infusion (methylprednisolone 120 mg/day) for 5 days were administered, with mild improvement of neurological symptoms within a week. Upon discharge, he was able to walk using a walker.

These cases provide further evidence of COVID-19-associated ACAM syndrome characterised by a generalised action myoclonus and ataxia, enriching the existing SARS-CoV-2-related literature on hyperkinetic movement disorders and gait disturbance.⁴

The subacute onset after SARS-CoV-2 infection, in addition to this distinct phenotype and the significant response to immunotherapy, points toward a post-infectious autoimmune encephalitis.⁵ As regards the pathophysiological mechanisms underlying post-infectious immune-mediated neurological disorders, several hypotheses have been put forward, including molecular mimicry-driven autoimmune process.⁴ In the case of SARS-CoV-2, the spike protein interacts with the ganglioside dimers for anchoring the cell surface and, due to cross-reactivity, an antibody-mediated response against structurally identical glycans on nerve gangliosides is triggered, thereby causing post-infectious myoclonus.⁴

Similar description of ACAM associated with SARS-CoV-2 has been reported, but with some differences.³ As in our patients,

all described cases in literature were male, aged 44–83 years, with ACAM onset after ten days from the first COVID-19 positive swab, and with a striking clinical improvement with steroids and/or immunoglobulin.³ Differently, in our patients opsoclonus was absent.

In conclusion, recognising central or peripheral neurological manifestations associated with SARS-CoV-2 infection is important in clinical practice and even more in patients without respiratory failure, since an early management allows a rapid improvement with a reduction of possible related disability. Further research and extensive data collection will contribute to clarify the causal relationship between SARS-CoV-2 infection and the post-infectious myoclonic syndrome either as a new phenomenon or as part of the ACAM spectrum.

CONFLICT OF INTERESTS

The authors have no conflicts of interest to declare.

STATEMENT OF AUTHORSHIP

I.M., M.M., and F.C. designed and oversaw the study. I.M., V.R., M.M., S.N., and F.C. recruited participants and described clinical syndromes. A.F.G. performed the primary interpretation of the data. A.F.G. and M.M. wrote the manuscript. F.V., P.V., S.M., and A.P., made major contributions to manuscript editing. All authors contributed to and critically reviewed the final version of the manuscript.

SUPPLEMENTARY MATERIAL

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REFERENCES

1. Paterson RW, Brown RL, Benjamin L, et al. The emerging spectrum of COVID-19 neurology: clinical, radiological and laboratory findings. *Brain*. 2020;143:3104–20. DOI [10.1093/brain/awaa240](https://doi.org/10.1093/brain/awaa240).
2. Khoo A, McLoughlin B, Cheema S, et al. Postinfectious brainstem encephalitis associated with SARS-CoV-2. *J Neurol Neurosurg Psychiatry*. 2020;91:1013–4. DOI [10.1136/jnnp-2020-323816](https://doi.org/10.1136/jnnp-2020-323816).
3. Foucard C, San-Galli A, Tarrano C, Chaumont H, Lannuzel A, Roze E. Acute cerebellar ataxia and myoclonus with or without opsoclonus: a parainfectious syndrome associated with COVID-19. *Eur J Neurol*. 2021;28:3533–6. DOI [10.1111/ene.14726](https://doi.org/10.1111/ene.14726).
4. Latorre A, Rothwell JC. Myoclonus and COVID-19: a challenge for the present, a lesson for the future. *Mov Disord Clin Pract*. 2020;7:888–90. DOI [10.1002/mdc3.13103](https://doi.org/10.1002/mdc3.13103).
5. Rábano-Suárez P, Bermejo-Guerrero L, Méndez-Guerrero A, et al. Generalized myoclonus in COVID-19. *Neurology*. 2020;95:e767–72. DOI [10.1212/WNL.0000000000009829](https://doi.org/10.1212/WNL.0000000000009829).