Myoclonus-Ataxia Syndrome Associated with COVID-19

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ABSTRACT

Neurological manifestations of coronavirus disease (COVID-19) have increasingly been reported since the onset of the pandemic. Herein, we report a relatively new presentation. A patient in the convalescence period following a febrile illness with lower respiratory tract infection (fever, myalgia, nonproductive cough) presented with generalized disabling myoclonus, which is phenotypically suggestive of brainstem origin, along with additional truncal cerebellar ataxia. His neurology work-ups, such as brain MRI, electroencephalography, serum autoimmune and paraneoplastic antibody testing, were normal. His CT chest scan revealed right lower lung infiltrates, and serological and other laboratory testing did not show evidence of active infection. COVID-19 titers turned out to be strongly positive, suggestive of post-COVID-19 lung sequelae. He responded partially to antimyoclonic drugs and fully to a course of steroids, suggesting a para- or postinfectious immune-mediated pathophysiology. Myoclonus-ataxia syndrome appears to be a neurological manifestation of COVID-19 infection, and knowledge regarding this phenomenon should be increased among clinicians for better patient care in a pandemic situation.

Key Words COVID-19; Myoclonus; Gait ataxia.

CASE REPORT

A 41-year-old male from Tamil Nadu state, India, had a history of febrile illness with myalgia and dry cough for approximately 1 week; he was nonalcoholic. He was treated only with oral paracetamol for fever at a local hospital [he had no history of using any drugs causing myoclonus at presentation or in the recent past (e.g., quinolones, cephalosporins, antiviral agents such as lopinavir or ritonavir, tramadol, antidepressants)]. Upon resolution of the abovementioned symptoms by approximately day 10, he noted subtle jerky involuntary movements of the limb along with difficulty while walking. His symptoms peaked over the next 10 days when he had severe limb and truncal jerking at rest that worsened upon action. He could not walk without support. He did not complain of any headache, cognitive symptoms, speech problems or any other neurological symptoms.

On examination at presentation (20 days post fever, 10 days post onset of neurological symptoms), the patient was alert and oriented; his score on the Mini-Mental Status Examination (MMSE) was 26/30. His cranial nerves were normal. His neurological examination revealed generalized myoclonus, which was pheno-typically suggestive of brainstem origin, along with additional truncal cerebellar ataxia. There was no evidence of extrapyramidal dysfunction or parkinsonism. His deep tendon reflexes were brisk with upgoing plantar responses. His sensory system was intact.

His laboratory investigations were normal. His cerebrospinal fluid analysis was normal except for a mildly decreased lymphocyte count (50%). His serum autoimmune and paraneoplastic antibody testing was negative. His MRI brain and spinal cord were normal. His electroencephalogram showed generalized background slowing with multifocal sharp and slow waves. His CT chest scan revealed right lower lung infiltrates. His serological and other laboratory testing did not show evidence of active infection. COVID-19 titers turned out to be strongly positive, suggestive of post-COVID-19 lung sequelae.

He responded partially to antimyoclonic drugs and fully to a course of steroids, suggesting a para- or postinfectious immune-mediated pathophysiology. Myoclonus-ataxia syndrome appears to be a neurological manifestation of COVID-19 infection, and knowledge regarding this phenomenon should be increased among clinicians for better patient care in a pandemic situation.

Key Words COVID-19; Myoclonus; Gait ataxia.
was 29/30. The patient predominantly had generalized myoclonus (mostly synchronous, both positive and negative) that was most prominent in the proximal upper and lower limbs and trunk, with auditory and mantle area tactile stimulus sensitivity. Clinically, myoclonus appeared to be a subcortical-brainstem origin phenotype. The patient had gait ataxia with normal upper and lower limb coordination, motor power, deep tendon reflexes and sensory examination, as well as possible gait disturbance due to myoclonus involving the proximal lower limb and trunk (Supplementary Video 1 in the online-only Data Supplement). The rest of the examination, including smell, speech, and eye movements, was within normal limits.

At this juncture, the likely pathophysiologies considered were brainstem encephalitis (in view of a predominant brainstem myoclonus-ataxia clinical syndrome) of direct viral, para/postinfectious or a primary autoimmune cause, as there was no history suggestive of other etiologies, such as drugs or hypoxic insult. Contrast MRI of the brain (Supplementary Figure 1 in the online-only Data Supplement), cerebrospinal fluid biochemistry and cytology were normal. Somatosensory evoked potentials (SSEPs) did not show any giant potential, and EEG did not reveal any epileptiform discharges. Detailed neuropsychology evaluation showed mild frontal dysfunction. In view of the current pandemic and a suspicious recent febrile history, a CT scan was performed on the chest, which showed right lower lobe ground glass opacities and associated interstitial thickening suggestive of a resolved viral lung infection (Figure 1). Reverse transcriptase polymerase chain reaction test for COVID-19 was predictably negative due to late presentation. His other serum markers, including D-dimer, ferritin, lactate dehydrogenase, and C-reactive protein, were within normal limits. An anti-COVID-19 antibody test was performed to rule out a recent COVID-19 infection. The IgG titer was 45.2, which was strongly positive (reference > 1 implies positive for COVID-19 infection), supporting the diagnosis of a recent COVID-19 infection. In view of the latent period of approximately 10 days for the onset of the neurological symptoms following the onset of fever, the likelihood of para/post infectious brainstem encephalitis-related myoclonus-ataxia syndrome was considered.

The patient was treated with clonazepam and levetiracetam with mild improvement in symptoms over the first 3 days of treatment with significant residual disability. He was subsequently treated with 1 g intravenous methylprednisolone (IVMP) for 5 days with significant improvement in symptoms. At discharge on day 10 of admission, the patient could walk easily without support (Supplementary Video 2 in the online-only Data Supplement). At the last outpatient follow-up at 6 weeks, the patient had complete resolution of ataxia and near total resolution of myoclonus while on 0.5 mg per day of clonazepam alone (levetiracetam was tapered off following discharge), with normal scores on the MMSE and Frontal Assessment Battery. Detailed neuropsychology evaluations could not be repeated.

**DISCUSSION**

As COVID-19 infection has been shown to have multisystemic manifestations, awareness among neurologists/general physicians/intensivists about the neurological manifestations of COVID-19 should be increased. The well-known COVID-19-related neurological syndromes described by various groups include encephalitis, meningitis, anosmia, GBS, ADEM, and acute cerebrovascular events. Myoclonus-ataxia spectrum syndrome following COVID-19 infection appears to be another neurological manifestation, as observed in a few recent case reports that had similar phenotypes, as listed in Table 1. Our patient also presented with this phenomenon of myoclonus-ataxia syndrome with onset approximately 10 days following a probable COVID-19 infection (supported by history of a recent febrile illness with cough, predominant right lung infiltrates on CT chest and strongly positive anti-COVID-19 IgG titer). In the context of the recent probable COVID-19-related febrile illness followed by a neurological syndrome within 6 weeks, the diagnosis of COVID-19-related myoclonus-ataxia syndrome is very likely in the absence of any hypoxic injury, absence of exposure to culpable drugs, and an unrevealing detailed work-up.

The anatomical substrate of myoclonus is likely to be subcortical in our case, as he predominantly had generalized myoclonus, mostly synchronous, both positive and negative, most prominent in the proximal upper and lower limbs and trunk, with auditory and mantle area tactile stimulus sensitivity with normal brain imaging, SSEP and EEG.

In recent similar case reports (detailed in Table 1), myoclonus has also been generalized, which affects proximal muscles of the limb and trunk with auditory and tactile stimulus sensitivity in
most cases, suggestive of brainstem origin. One group showed an absence of jerk-locked cortical potential on backaveraging, supporting the anatomical localization of myoclonus to subcortical origin.5

Our patient additionally had probable pure truncal ataxia, which could be related to vermian involvement, although gait issues could also be additionally attributable to truncal and proximal lower limb myoclonus. This is not surprising, as the neurological spectrum of COVID-19 infection is very vast and ever expanding. There has been a recent case report of opsoclonus myoclonus ataxia syndrome following COVID-19.9

<table>
<thead>
<tr>
<th>Study</th>
<th>Cases (age in years, sex)</th>
<th>Lung involvement</th>
<th>Latency to onset of neurological symptoms from onset of systemic symptoms related to COVID-19</th>
<th>Neurological features</th>
<th>Treatment and response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rábano-Suárez et al.4</td>
<td>Case 1: 63, M</td>
<td>Case 1: Bilateral pneumonia, mechanically ventilated Case 2: Bilateral pneumonia Case 3: Bilateral pneumonia</td>
<td>Case 1: 9 days Case 2: 3 weeks Case 3: 11 days</td>
<td>Case 1: anosmia; myoclonic storm, more involving upper half of body; auditory and tactile stimulus sensitive; somnolence Case 2: anosmia, mild myoclonus, mild hypersomnia Case 3: anosmia, mild myoclonus</td>
<td>Case 1: LEV, CLN, IVMP 1g/day for 5 days. PLEX × 5 cycles. Patient had sustained improvement only after PLEX. Case 2: resolved with IVMP 250 mg/day for 3 days Case 3: LEV, CLN, IVMP 250 mg/day for 3 days. Patient had delayed improvement after 2 weeks.</td>
</tr>
<tr>
<td>Muccioli et al.5</td>
<td>58, M</td>
<td>Respiratory distress, mechanically ventilated HCQ, tocilizumab remdesivir given</td>
<td>3 weeks</td>
<td>Brief agitation for 2 days-self resolved followed by multifocal myoclonus: action and tactile stimulus sensitive; diffuse, but more prominent in right proximal lower limb - causing marked disability to stand</td>
<td>Symptoms resolved completely with symptomatic treatment with CLN and LEV in 5 days.</td>
</tr>
<tr>
<td>Khoo et al.6</td>
<td>65, F</td>
<td>Bilateral lung infiltrates seen</td>
<td>7 days</td>
<td>Patient had baseline Alzheimer’s disease Unilateral onset of myoclonus generalised within 2 days, stimulus sensitive, with hyperkplexia to tactile, visual and auditory stimulus Noted cognitive decline: language difficulties, visual hallucination</td>
<td>IVMP 1 g/day for 3 days followed by oral steroid taper with prednisolone Patient had significant improvement in cognition and myoclonus. Cognition improved to baseline. Myoclonus had not completely resolved at discharge (follow up till day 10 from start of steroids)</td>
</tr>
<tr>
<td>This study</td>
<td>41, M</td>
<td>Predominant right lower lung infiltrates</td>
<td>10 days</td>
<td>Generalised severe myoclonus predominantly proximal, involving limbs and trunk, present at rest and on action, auditory and tactile stimulus sensitivity present, truncal ataxia noted Mild frontal dysfunction noted on detailed neuropsychology evaluation</td>
<td>Noted moderate benefit with LEV and CLN IVMP 1 g/day given for 5 days -continued to improve</td>
</tr>
</tbody>
</table>

been variable in the cases reported until now. Our patient improved significantly (> 75%) with antmyoclonic drugs and a 5-day course of IVMP. Although all reported cases have significantly improved, the speed of recovery has been variable. There also has been variable response to available medications—some have responded very well to only anti-myoclonic medication, whereas some had to escalate the therapy to plasma exchange due to lack of benefit with anti-myoclonic and steroid medications.4,6

The pathophysiology of neurological findings, in the current case and similar recently reported cases, is more likely to be para- or postinfectious in view of the onset of neurological symptoms in the 2nd or 3rd week from the onset of febrile illness, with a monophasic course and resolution of the symptoms in the subsequent weeks. It is difficult to conclude whether the improvement occurred as a part of the natural course of disease or due to medications. Alternate pathophysiology could be direct transneural spread of the virus to the central nervous system through the olfactory tract, especially in view of hyposmia at the onset of viral fever. Other pathophysiology, such as hypoxia-related or any culpable drug, were ruled out in the abovementioned cases. As noted in our case, this syndrome does not appear to have any consistent correlation with the severity of COVID-19 infection or the presence of cytokine release syndrome or any specific laboratory parameter derangement [enlisted in Supplementary Table 1 (in the online-only Data Supplement)].10

Brainstem myoclonus-ataxia syndrome appears to be another addition to the spectrum of COVID-19-related neurological manifestations. Its pathophysiology is mostly para/post infectious phenomenon. Although the response to medications seems to be variable, the overall prognosis appears to be fair.

Ethics Statement
Informed consent was obtained from patient for using his video (without masking) for publication purpose.

Supplementary Video Legends
Video 1. At initial presentation, patient predominantly had generalized myoclonus (mostly synchronous, both positive and negative) that was most prominent in the proximal upper and lower limbs and trunk, with auditory and mantle area tactile stimulus sensitivity along with gait ataxia.

Video 2. Patient had marked resolution of symptoms at discharge on day 10 after treatment with intravenous methylprednisolone, clonazepam and levetiracetam.

Supplementary Materials
The online-only Data Supplement is available with this article at https://doi.org/10.14802/jmd.20106.

Conflicts of Interest
The authors have no financial conflicts of interest.

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None.

Author Contributions
Conceptualization: Kuldeep Shetty, Atul Manchakrao Jadhav, Ranjith Jayanthakumar. Data curation: all authors. Formal analysis: all authors. Funding acquisition: Kuldeep Shetty, Atul Manchakrao Jadhav, Ranjith Jayanthakumar, Gopal Krishna Dash, Radhika Manohar, Vivek Jacob Philip, Vikram Huded. Investigation: all authors. Methodology: all authors. Project administration: Kuldeep Shetty, Atul Manchakrao Jadhav, Ranjith Jayanthakumar. Resources: all authors. Software: Kuldeep Shetty, Atul Manchakrao Jadhav, Ranjith Jayanthakumar. Supervision: Kuldeep Shetty, Atul Manchakrao Jadhav, Ranjith Jayanthakumar. Validation: all authors. Visualization: all authors. Writing—original draft: all authors. Writing—review & editing: all authors.

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REFERENCES
Supplementary Figure 1. MRI brain with contrast was normal. Above figure shows the normal FLAIR and T1 contrast sequences in axial and coronal sections.
**Supplementary Table 1.** Details of investigational work up in the reported cases

<table>
<thead>
<tr>
<th></th>
<th>Rábano-Suárez et al.⁴</th>
<th>Muccioli et al.⁵</th>
<th>Khoo et al.⁶</th>
<th>This study</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MRI Brain</strong></td>
<td>Normal</td>
<td>Moderate SVID</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td><strong>CSF cytology and biochemistry</strong></td>
<td>Case 1: normal</td>
<td>Mildly elevated proteins</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td></td>
<td>Case 2, 3: not done</td>
<td>CSF IL-6 elevated</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>SSEP</strong></td>
<td>-</td>
<td>-</td>
<td></td>
<td>No giant potentials</td>
</tr>
<tr>
<td><strong>EEG</strong></td>
<td>-</td>
<td>Normal on backaveraging</td>
<td>-</td>
<td>Normal</td>
</tr>
<tr>
<td><strong>CNS autoimmune/paraneoplastic serology</strong></td>
<td>Case 1 &amp; 3 -negative</td>
<td>Negative</td>
<td>Negative (including anti DPPX ab &amp; anti glycine R ab)</td>
<td>Negative</td>
</tr>
<tr>
<td><strong>Airway RT-PCR during acute infectious stage</strong></td>
<td>-</td>
<td>Positive</td>
<td>Positive</td>
<td>-</td>
</tr>
<tr>
<td><strong>CSF RT-PCR</strong></td>
<td>-</td>
<td>Negative</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><strong>CSF IL-6</strong></td>
<td>-</td>
<td>Elevated</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><strong>IgG</strong></td>
<td>-</td>
<td>Elevated</td>
<td>-</td>
<td>45.2; strongly positive Cut off &gt;1 implies positive</td>
</tr>
<tr>
<td><strong>CRP</strong></td>
<td>Normal</td>
<td>-</td>
<td>Elevated</td>
<td>Normal</td>
</tr>
<tr>
<td><strong>D-dimer</strong></td>
<td>Elevated</td>
<td></td>
<td>Elevated</td>
<td>Normal</td>
</tr>
<tr>
<td><strong>Ferritin</strong></td>
<td>Elevated in case 3</td>
<td>-</td>
<td>-</td>
<td>Normal</td>
</tr>
<tr>
<td><strong>LDH</strong></td>
<td>Mildly elevated in case 2, 3</td>
<td>-</td>
<td>-</td>
<td>Normal</td>
</tr>
</tbody>
</table>