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CASE REPORT

Autonomic dysfunction heralding acute motor axonal neuropathy in COVID-19

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Abstract

Albeit primarily a disease of respiratory tract, the 2019 coronavirus infectious disease (COVID-19) has been found to have causal association with a plethora of neurological and neuropsychological effects. However, the pathogenesis of COVID-19-induced neurological manifestations is still in its infancy. Autonomic dysfunction preceding acute motor axonal neuropathy (AMAN) has not been yet associated with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. We herein report one patient who developed acute onset dysautonomia heralding AMAN during SARS-CoV-2 infection.

Keywords Autonomic dysfunction · Acute motor axonal neuropathy · COVID-19 · SARS-CoV-2

Physicians are seeing increasingly more patients with a spectrum of neurological manifestations associated with coronavirus disease 2019 (COVID-19) (Ghosh et al. 2020; Gutiérrez-Ortiz et al. 2020; Rábano-Suárez et al. 2020; Roy et al. 2020). However, the pathogenesis of COVID-19-induced neurological manifestations is still in its infancy. Autonomic dysfunction preceding acute motor axonal neuropathy (AMAN) has not been yet associated with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. We herein report one patient who developed acute onset dysautonomia heralding AMAN during SARS-CoV-2 infection.

Case report A 20-year-old man was admitted to the emergency room with rapidly progressive weakness of all four limbs over a period of 3 days. His past medical history was unremarkable. Eight days prior to his admission, he had developed a mild fever, sore throat, and generalized malaise. He also complained of intermittent severe dizziness, profuse sweating, constipation, erectile dysfunction, and a feeling of shivering cold and central chest discomfort since last 5 days.

On physical examination, he was fully awake, conscious, anxious, afebrile, hypertensive (recorded supine blood pressure was 180/96 mm of Hg), and tachycardic. Postural drop of blood pressure was noted when he was made to stand up from supine recumbent position with support. His respiratory rate was 16/min and oxygen saturation of 98% in room air. Bedside electrocardiogram monitoring showed loss of sinus arrhythmia without any ischemic changes. Valsalva maneuver was positive for autonomic dysfunction as there was loss of heart rate variability and reflex blood pressure changes. Isometric hand grip exercise failed to demonstrate response of autonomic stability, as there was no increase in heart rate. Patient had abnormal bedside thermoregulatory sweat testing and cold pressor test. Neurological examination revealed generalized hypotonia without any wasting and fasciculation. Muscle power estimation by MRC scale showed 1/5 in proximal and 3/5 in distal superior extremities and 1/5 in proximal and 2/5 in distal inferior extremities. All the deep tendon reflexes were absent.

The patient's nasopharyngeal swab test for SARS-CoV-2 by qualitative real-time reverse-transcriptase–polymerase-chain-reaction (RT-PCR) assay was positive. Blood analysis was remarkable for lymphocytopenia. MRI of the brain and

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cervical spine were normal. Nerve conduction studies of all four limbs revealed reduced compound motor action potential amplitudes in bilateral median, ulnar, peroneal, and tibial nerves with normal distal latencies and conduction velocities. F-wave latencies were absent in all four limbs (Table 1). The electromyogram showed abundant spontaneous muscle activity in proximal and distal muscles of the upper and lower limbs with a reduced recruitment pattern suggestive of AMAN. Tests for hepatitis B and C, HIV, *Campylobacter jejuni*, *Haemophilus influenzae*, *Cytomegalovirus*, and Epstein-Barr virus infection were all negative. Anti-ganglioside antibodies were not found in serum. The cerebrospinal fluid (CSF) examination revealed albuminocytological dissociation (white blood cell count = 6/μl and protein = 180 mg/dl). Contrast enhanced CT scan of thorax was unremarkable.

As COVID-19-related illness was mild and almost asymptomatic, he was just treated with acetaminophen. For AMAN, intravenous immunoglobulin (0.4 g/kg/day for 5 days) was started, and after 15 days of therapy, his motor deficits and dysautonomia started improving. With rigorous physiotherapy he was able to walk with some assistance at 1 month of hospital admission.

Discussion SARS-CoV-2 has potential for neurotropism (Li et al. 2020; Rábano-Suárez et al. 2020; Roy et al. 2020). Study with animal models have demonstrated that SARS-CoV and MERS-CoV, possibly via olfactory nerves, can spread rapidly inside central nervous system, thalamus and brainstem in particular (Li et al. 2020). However, the pathogenesis of clinical manifestations associated with SARS-CoV-2 still needs to be elucidated.

Reports of the association of Guillain-Barré syndrome (GBS) with COVID-19 infection have been published worldwide (Sedaghat and Karimi 2020; Toscano et al. 2020; Virani et al. 2020; Zhao et al. 2020), including all variants of GBS and a case of AMAN (Toscano et al. 2020), as well as one case of Miller Fisher Syndrome and another one of polyneuritis cranialis (Gutierrez-Ortiz et al. 2020). Pathogenetic mechanisms for GBS may be either mediated by direct neurotropism or aberrant immune mediated injury. Evidences are lacking in favor of direct neuroinvasion in case of GBS as substantiated by negativity of RT-PCR for SARS-CoV-2 in CSF (Gutierrez-Ortiz et al. 2020). Toscano et al. (2020) reported that three patients who were tested for anti-ganglioside antibodies were negative (Toscano et al. 2020); by contrast, Gutiérrez-Ortiz et al. (2020) found serum anti-GD1b-IgG antibodies in a patient with Miller Fisher Syndrome, supporting immune-regulated injury rather than direct viral neuropathic effects. In our patient, anti-ganglioside antibodies were negative.

Unlike all other previously published cases on COVID-19 associated with GBS, our patient had preceding autonomic dysfunction in the form of sinus arrhythmia, postural hypotension, intermittent profuse sweating, constipation, erectile dysfunction, and squeezing sensation in the chest. This is something unique in this case in addition to the fact that autonomic dysfunction preceded motor weakness, which is exceedingly rare. Though dysgeusia and hyposmia/anosmia are considered to be two significant early symptoms of harboring COVID-19 (Gutierrez-Ortiz et al. 2020; Rábano-Suárez et al. 2020), our patient did not have any of these symptoms, unlike patients of series by Toscano et al. (2020).

We recognize that the main limitation was that we could not arrange for tilt-table test for this patient to measure severity of postural hypotension. The reason for this was the extreme circumstances in our hospital at the peak of this pandemic.

To conclude, GBS and its variants are quite uncommon neurological presentation of COVID-19. Lesson from

Table 1 Nerve conduction study parameters

Nerve stimulated	Stimulation site	Amplitude		Latency (ms)		Conduction velocity		F-wave	
		Right	Left	Right	Left	Right	Left	Right	Left
Median (s)	Wrist	34.3 μV	38.2 μV	2.9 ms	2.7 ms	54.2 m/s	56.1 m/s		
Ulnar (s)	Wrist	28.3 μV	29.8 μV	2.4 ms	2.3 ms	58.1 m/s	56.9 m/s		
Sural (s)	Calf	15.8 μV	18.7 μV	2.3 ms	2.4 ms	42.2 m/s	42.8 m/s		
Median (m)	Wrist	3.1 mV	2.1 mV	2.7 ms	3.1 ms	58.2 m/s	61.2 m/s	NR	NR
	Antecubital fossa	2.2 mV	1.3 mV	7.3 ms	7.1 ms			NR	NR
Ulnar (m)	Wrist	1.7 mV	2.2 mV	2.1 ms	2.3 ms	54.3 m/s	56.2 m/s	NR	NR
	Below elbow	1.1 mV	1.5 mV	5.6 ms	5.8 ms			NR	NR
	Above elbow	0.9 μV	1.3 mV	6.2 ms	6.4 ms			NR	NR
Tibial (m)	Ankle	0.9 μV	0.8 μV	5.2 ms	5.3 ms	42.3 m/s	44.7 m/s	NR	NR
	Popliteal fossa	0.5 μV	0.5 μV	5.6 ms	4.9 ms				
Peroneal (m)	Ankle	NR	NR	NR	NR	NR			

m motor study, *s* sensory study, *NR* no response

previous reports shows GBS, and its variants, may result from COVID-19 infection. Regarding treatment, data showed outcome to be no way different from GBS following other infections.

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Compliance with ethical standards

Conflict of interest R. Ghosh, D. Ray, and S. Sengupta report no relevant disclosures. J. Benito-León is supported by the National Institutes of Health, Bethesda, MD, USA (NINDS #R01 NS39422), European Commission (grant ICT-2011-287739, NeuroTREMOR), the Ministry of Economy and Competitiveness (grant RTC-2015-3967-1, NetMD—platform for the tracking of movement disorder), and the Spanish Health Research Agency (grant FIS PI12/01602 and grant FIS PI16/00451).

Appendix. Authors

Name	Location	Contribution
Ritwik Ghosh, MD	Department of General Medicine, Burdwan Medical College & Hospital, Burdwan, West Bengal, India	Conception, organization, and execution of the research project; writing of the first draft and the review and critique of the manuscript
Dipayan Roy, MD	Department of Biochemistry, AIIMS Jodhpur, Jodhpur, Rajasthan, India	Conception and organization of the research project; review and critique of the manuscript
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