Temporal association between SARS-CoV-2 and new-onset myasthenia gravis: is it causal or coincidental?

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SUMMARY
Several case reports of COVID-19 in patients with myasthenia gravis (MG) have been documented. However, new-onset autoimmune MG following COVID-19 has been reported very rarely. We report one such case here. A 65-year-old man presented to us with dysphagia 6 weeks following mild COVID-19. He was evaluated and diagnosed as antiacetylcholine receptor antibody (AchR) positive, non-thymomatous, generalised MG. He subsequently developed myasthenic crisis and improved after treatment with intravenous immunoglobulin, prednisolone and pyridostigmine. Systematic literature review showed eight more similar cases. Analysis of all cases including the one reported here showed these features: mean age 55.8 years, male gender (5), time interval between COVID-19 and MG (5–56 days), generalised (5), bulbar and/or ocular symptoms (4), anti-AchR antibodies (7) and antimuscle-specific kinase antibodies (2). All have improved with immunotherapy. Although, many hypothesis are proposed to explain causal relationship between the two, it could as well be sheer coincidence.

BACKGROUND
COVID-19 pandemic is caused by highly infectious SARS-CoV-2. Observational studies have documented several neurological complications or associations either during or after COVID-19. However, direct causality is uncertain. Several case reports and series of COVID-19 in patients with myasthenia gravis (MG) have been documented; in some patients, COVID-19 had worsened the myasthenic weakness resulting in myasthenic crisis and improved after treatment with intravenous immunoglobulin, prednisolone and pyridostigmine. Systematic literature review showed eight more similar cases. Analysis of all cases including the one reported here showed these features: mean age 55.8 years, male gender (5), time interval between COVID-19 and MG (5–56 days), generalised (5), bulbar and/or ocular symptoms (4), anti-AchR antibodies (7) and antimuscle-specific kinase antibodies (2). All have improved with immunotherapy. Although, many hypotheses are proposed to explain causal relationship between the two, it could as well be sheer coincidence.

DIFFERENTIAL DIAGNOSIS
We considered the following differential diagnosis in that order of priority after the clinical examination. First, we speculated the possibility of a pharyngocervicobrachial variant of Guillain-Barré syndrome (1). Intra-thoracic myasthenia (2) and immune MG following COVID-19 and review the current literature.

CASE PRESENTATION
A 65-year-old man, a known patient of diabetes and hypertension, presented to us with dysphagia in the third week of October 2020. He was diagnosed with mild COVID-19 (nasopharyngeal swab positive for SARS-CoV-2 reverse transcriptase-PCR, RT-PCR) in the first week of September 2020. He was treated with intravenous remdesivir and other supportive therapy. Repeat RT-PCR done in the third week of September was negative. Six weeks after the onset of COVID-19, he developed acute-onset dysphagia for both solids and liquids, which progressed in the subsequent 2 days. He did not report diurnal variation. General examination was unremarkable. Speech showed nasal intonation. Cranial nerve examination showed normal visual acuity, ocular motility, pupillary size and reactivity, mild bifacial weakness, decreased bilateral palatal movements and poor pharyngeal reflex. Motor and sensory examination, deep tendon reflexes, cerebellar and gait examination were normal.

INVESTIGATIONS
MRI of the brain and spinal cord was normal. NCS showed reduced sensory nerve action potential and sensory conduction velocity of ulnar and sural nerves with normal motor nerve conduction parameters suggestive of mild sensory neuropathy. Slow repetitive nerve stimulation (RNS) of nasalis (41%) and trapezius (18.1%) showed a significant decremental response (figure 1). Intravenous neostigmine showed marked improvement in swallowing. Serum antiacetylcholine receptor antibody (AchR) titres were 4.5 nmol/L (<0.40: negative). Serum antimuscle-specific kinase (MuSK) antibody titres were less than 0.18 U/L (<0.40: negative). The SARS-CoV-2 IgG ECLIA antibody titres (Roche diagnostics, USA) were 129 (<1.0: non-reactive). Thyroid function tests were normal. High-resolution CT of the thorax did not reveal thymic hyperplasia or thymoma.

Figure 1 Decremental response in slow RNS (3 Hz) of left trapezius. RNS, repetitive nerve stimulation.

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Table 1 Characteristics of 10 cases of post COVID-19 autoimmune myasthenia gravis (MG)

| Author          | Age/ gender | Comorbidities and family history | COVID symptoms | COVID Severity | CT chest | COVID-19 treatment | Duration between COVID-19 and MG (in days) | MG type | Thymus pathology | Antibody | SARS-CoV-2 ab lgG titre | Treatment | MG Treatment | Outcome | Complications |
|-----------------|-------------|----------------------------------|----------------|---------------|----------|--------------------|-------------------------------------------|---------|-------------------|----------|---------------------|-----------|--------------|---------|---------------|
| Restivo et al   | 64/M        | None                             | Fever          | Mild          | Normal   | NA                 | 5                                         | Generalised | None              | AchR     | NA                  | PSL (75 mg/d); Pyridostigmine (240 mg/d) | Improved | None          |
| 68/M            | None        | Fever                            | Mild           | Normal        | NA       | 7                  | Generalised                               | None      | AchR              | NA       | IVIG (0.4 kg/d x 5 days) | PLEX      | Improved      | None |
| 71/F            | None        | Cough Fever                       | Severe         | Bilateral     | Interstitial Pneumonia | 5 | Generalised | None | AchR | NA | Pyridostigmine (240 mg/d) | Improved | Septic Shock; Dysautonomia (Bradycardia) |
| Sriwastava et al| 65/F        | Left RCC (S/P nephrectomy) Pituitary adenoma (S/P resection) Pulmonary Carcinoid Meningioma Old Pulmonary Embolism | Diarrhoea Myalgia | Severe | Bilateral Consolidation | Convalescent Plasma; Dexamethasone | 11 | Ocular symptoms only | None | AchR | NA | Pyridostigmine (240 mg/d) | Improved | |
| Pérez Álvarez et al | 48/M  | Paranoid Schizophrenia Inverse Psoriasis Positive ANA | Fever | Mild | Bilateral Consolidation | AZM; HCQS | 15 | Ocular symptoms only | None | AchR | NA | NA | Improved | None |
| Huber et al     | 21/F        | Family history of Hashimoto's thyroiditis Addison's disease Pernicious anaemia | Cold Fatigue Anosmia Ageusia Diarhoea | Mild | Normal | None | 15 | Ocular symptoms only | None | AchR | Positive | IVIG (0.4 kg/d x 5 days); Pyridostigmine (180 mg/d) | Improved | None |
| Assini et al    | 77/M        | None                             | Fever | Cold | Dyspnoea | NA | Bilateral Consolidation | NA | Oculobulbar symptoms only | None | MuSK | NA | Pyridostigmine (240 mg/d) | AZT (1.5 mg/kg) | Improved | None |
| Muhammed et al  | 24/F        | None                             | Influenza like syndrome | Mild | NA | None | 28 | Generalised | None | MuSK | Positive | IVIG PSL (2.5 mg/d) | Pyridostigmine | Improved | None |
| Our case        | 65/M        | Diabetes Hypertension            | Fever, Cold | and Cough | Mild | Normal | Remdesivir | 42 | Generalised | None | AchR | 129 | IVIG, PSL, AZT Pyridostigmine | Improved | None |

AchR, acetylcholine receptor antibody; ANA, antinuclear antibodies; AZM, Azithromycin; AZT, Azathioprine; f, female; HCQS, Hydroxychloroquine sulfate; IVIG, Intravenous immunoglobulin; M, male; MuSK, Muscle-specific kinase; NA, not available; PLEX, plasma exchange; PSL, prednisolone; RCC, Renal cell carcinoma.
syndrome (GBS) given the presentation with bulbar symptoms and recent history of COVID-19. Multiple case reports and series of GBS and variants following COVID-19 are published. However, the absence of arm and neck weakness at presentation, preserved deep tendon reflexes, absence of demyelination on Nerve conduction studies (NCS) and decremental response on RNS ruled out GBS. Moreover, dramatic clinical response to intravenous neostigmine is also at odds with GBS. Second, botulism was considered. However, the absence of history suggestive of canned or stored food ingestion and further clinical course negated this. Third, central causes like stroke or brain stem demyelination were considered. However, the absence of pyramidal and/or cerebellar signs, preserved sensorium and normal brain imaging ruled out these diseases.

**TREATMENT**

He was started on oral prednisolone (30 mg/day) and oral pyridostigmine (60 mg every 6 hours). His MG Composite (MGC) score at admission 8. However, there was no improvement, and he needed intravenous neostigmine intermittently. On day 8 of admission, he developed neck and respiratory muscle weakness with a single breath count of eight (MGC 17). Arterial blood gas analysis showed type II respiratory failure (PCo2 52 mm Hg). Because of a myasthenic crisis, he was intubated and connected to a ventilator. Pyridostigmine was stopped, and prednisolone increased to 40 mg/day. He was treated with intravenous immunoglobulin (0.4 mg/kg/day) for five consecutive days. On day 10, he developed upper lip proximal weakness (MGC 33). Tracheostomy was done, anticipating more extended ventilator support on day 14. He showed improvement in neck and limb weakness from day 16 (MGC 31). He was later started on azathioprine (50 mg every 12 hours), pyridostigmine (60 mg every 6 hours) and prednisolone (40 mg every 24 hours) were continued.

**OUTCOME AND FOLLOW-UP**

With improved respiratory muscle function, he was decanulated on day 21, and an oral soft diet trial was given with a nasogastric tube in situ (MGC 19). He was discharged 2 days later with a nasogastric tube. The patient has been under outpatient follow-up since November 2020 until his bulbar function improved ultimately in the subsequent 2 weeks and oral feeds were resumed (MGC 0). Prednisolone (40 mg every 24 hours) was tapered after 2 months of stable course after discharge. He is currently on azathioprine (50 mg every 12 hours) and pyridostigmine (60 mg every 12 hours).

**DISCUSSION**

Autoimmune MG is a disease of neuromuscular junction caused by autoantibody-mediated destruction of the postsynaptic membrane and characterised clinically by fatigable weakness of skeletal muscles. Various immunosuppressant and immunomodulatory therapies are used in the treatment. Few reports showed new onset of MG occurring following varicella zoster, West Nile and Zika virus. Thus it is quite possible, MG occurring following COVID-19. To date, there were reports of eight such patients published in the literature. Clinical features of all nine patients, including one described in this report, are summarised in table 1. The Majority were aged above 50 years (67%) and suffered mild COVID-19 (75%). The interval between COVID-19 and MG ranged between 5 and 56 days. Five had generalised myasthenia, three had ocular symptoms only and one had oculobulbar symptoms only. None had thymic hyperplasia or thymoma. Seven had anti-AChR antibodies, and two had anti-MuSK antibodies. All have improved with immunotherapy. There are many plausible explanations for this causal association. First, antibodies against SARS-CoV-2 might cross-react with AChR and MuSK receptors due to molecular mimicry between the viral proteins and the postsynaptic proteins. The latent period between the COVID-19 and MG favours this hypothesis. Second, COVID-19 produces a proinflammatory milieu and cytokine storm leading to immune dysregulation and disrupted self-tolerance. Third, dormant MG might have been triggered by COVID-19 to become overtly symptomatic. Lastly, MG might be triggered by drugs like hydroxychloroquine sulfate and azithromycin prescribed often to treat COVID-19. On the contrary, this association might be sheer coincidental considering the vastly different incidence rates of the two diseases. MG is quite rare, with an annual incidence rate of 2.1–5.0 per 100 000 people. In conclusion, MG is a rare post-infectious complication of COVID-19. Longitudinal follow-up of such patients might provide additional insight into this unique link and natural course of the disease.

**Learning points**

- COVID-19 can trigger new-onset autoimmune myasthenia gravis.
- It is more common in elderly males with non-severe COVID-19 and has a good outcome.
- Plausible causal explanations include—molecular mimicry, loss of immunological self-tolerance following COVID-19, drug-induced exacerbation of occult myasthenia. However, this association might be a sheer coincidence.
- Long-term follow-up of these patients can give more insight into this unusual association.

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