Myasthenia Gravis Associated With COVID-19 Infection

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Abstract

COVID-19 first emerged in Wuhan, China in late December 2019. The disease majorly involves the lungs leading to various respiratory complications; however, neurological manifestations of the disease are also described in the literature. Here, we report a case of COVID-19–induced seronegative myasthenia gravis (MG). We discuss the cases of COVID-19 and MG already described in the literature in regard to their presentation and serological findings to better understand the association between the two disease processes. MG may be missed in patients after COVID-19 infections because of the comorbidities and anti-acetylcholine receptor and anti-muscle-specific tyrosine kinase antibodies being negative. Evidence from more studies will help analyze the pathological timeline of the disease process and the immunological characteristics of COVID-19–induced MG which can prove to have morbidity and mortality benefit in patients with COVID-19–induced MG.

Categories: Internal Medicine, Infectious Disease, Pulmonology
Keywords: covid-19, autoimmune, sars-cov-2, sars, coronavirus disease, coronavirus, myasthenia gravis (mg)

Introduction

COVID-19 emerged in Wuhan, China in December 2019. Major manifestations of COVID-19 are respiratory complications; however, neurological manifestations of the disease have also emerged over time [1]. Myasthenia gravis (MG) is an autoimmune condition with autoantibodies against the nicotinic acetylcholine receptors located at the neuromuscular junction [2]. Patients between the ages of 21 and 65 have been diagnosed with new-onset MG with positive anti-acetylcholine receptor (AChR) autoantibodies post-COVID-19 infection [3-5]. Moreover, cases of patients with anti-muscle-specific tyrosine kinase (MuSK)-MG have also been reported after COVID-19 infection [6].

Here, we report a case of COVID-19–induced seronegative MG with a review of cases already described to understand the association between the two disease processes.

Case Presentation

A 46-year-old male with a past medical history of hypertension, hyperlipidemia, morbid obesity (body mass index of 38 kg/m²), obstructive sleep apnea, pes excavatum, interstitial lung disease, and recent hospitalization five months earlier due to acute hypoxic respiratory failure secondary to COVID-19 infection requiring mechanical ventilation presented to the emergency department with worsening shortness of breath that started a few days ago. He stated that he had recent exposure to sick children and had developed shortness of breath and a dry cough for a few days. However, his viral panel and COVID-19 testing were negative on admission. His vitals on presentation were as follows: his blood pressure was 128/82 mmHg, heart rate was 95 beats per minute, the temperature was 99.7°F, respiratory rate was 26 breaths per minute, and oxygen saturation was 91% on 3 L of oxygen via a nasal cannula. A Chest X-ray showed bilateral opacities left greater than right (Figure 1).
FIGURE 1: Chest X-ray showing bilateral opacities left greater than right.

His pertinent laboratory values are listed in Table 1.

<table>
<thead>
<tr>
<th>Laboratory parameters</th>
<th>Value</th>
<th>Reference range</th>
</tr>
</thead>
<tbody>
<tr>
<td>White blood cell count</td>
<td>10.34 K/µL</td>
<td>4.80–10.80 K/µL</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>13.9 g/dL</td>
<td>14.0–18.0 g/dL</td>
</tr>
<tr>
<td>Platelet count</td>
<td>200 K/µL</td>
<td>130–400 K/µL</td>
</tr>
<tr>
<td>The partial pressure of carbon dioxide (arterial)</td>
<td>99 mmHg</td>
<td>42–55 mmHg</td>
</tr>
<tr>
<td>pH</td>
<td>7.27</td>
<td>7.32–7.43</td>
</tr>
<tr>
<td>Oxygen (arterial)</td>
<td>55 mmHg</td>
<td>80–100 mmHg</td>
</tr>
<tr>
<td>Serum bicarbonate</td>
<td>42 mmol/L</td>
<td>17–32 mmol/L</td>
</tr>
<tr>
<td>Anti-low-density lipoprotein receptor-related protein 4 antibody</td>
<td>Positive</td>
<td>Positive/negative</td>
</tr>
</tbody>
</table>

TABLE 1: Pertinent lab findings.

Shortly after presenting to the emergency department, the patient’s respiratory status worsened, and he was placed in non-invasive ventilation, despite which he showed no improvement. The arterial blood gas showed a worsening pH of 7.20, partial pressure of carbon dioxide of 127 mmHg, and his mental status started to decline. He was intubated shortly after and started on intravenous ceftriaxone and azithromycin for suspected bacterial pneumonia.

Over the following days, the critical care team found it difficult to wean the patient off mechanical ventilation as he continued to fail spontaneous breathing trials. He was also found to have proximal muscle weakness along with ptosis, so neurology was consulted for further evaluation. Anti-AChR autoantibodies and anti-MuSK-MG were negative. However, antibodies against lipoprotein-related protein 4 were positive suggesting double-seronegative MG. He was started on pyridostigmine 60 mg TID with good response and was extubated consequently. The patient underwent a CT scan which was negative for a thymoma.
Discussion

MG is a disease that causes localized or generalized muscle weakness due to antibodies not only against AChR and MuSK but other AchR-related proteins as well, which are located in the post-synaptic muscle membrane [7].

Infectious insults can trigger new-onset MG and other autoimmune diseases and cause disease deterioration [8]. SARS-CoV-2-induced autoimmune diseases including MG have been described in the literature [9]. COVID-19 seems to show an affinity for neural tissue as there have been reports of encephalitis, encephalopathy, cranial neuropathies, Guillain-Barré syndrome, rhabdomyolysis, anosmia, and ageusia [1]. Although the pathophysiology of COVID-19-induced MG has not been established yet, there are a few postulated mechanisms. These mechanisms include molecular mimicry as some COVID-19 proteins may be similar to human antigens [3-5,10-13] and an increased release of type 1 interferon and other inflammatory cytokines 14. Other hypothesized mechanisms include a breakdown of self-tolerance mechanisms after infection [11,12,14,15] and activation of latent MG 1 [4,15]. There have been a few cases of MG after COVID-19 [3-5,10-17], but to our knowledge, seronegative MG post-COVID-19 has not been described yet. It is important to recognize that seronegative MG can occur after COVID-19 as a delay in diagnosis can possibly worsen outcomes.

It is important to remember our patient received azithromycin which is not recommended in patients with underlying MG as it can worsen their condition [18]. This information coupled with the fact that our patient had a latency of 152 days between infection and MG onset raises the question of whether azithromycin worsened the patient’s subclinical, undiagnosed MG.

The details of the cases we reviewed are mentioned in Table 2.

<table>
<thead>
<tr>
<th>Author et al., 2020</th>
<th>Gender</th>
<th>Age</th>
<th>Days for myasthenia to present post-COVID-19</th>
<th>Repetitive stimulation test</th>
<th>Antibodies</th>
<th>Myasthenia type</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Restivo et al., 2020 [4] Male</td>
<td>64</td>
<td>5</td>
<td>Repetitive stimulation of the facial nerve showed a 57% decrement</td>
<td>Anti-AChR Abs+</td>
<td>Generalized MG</td>
<td>Responsive to pyridostigmine bromide and prednisone</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>71</td>
<td>5</td>
<td>Ulnar RNS 56% decrement</td>
<td>Anti-AChR Abs+</td>
<td>Generalized MG</td>
<td>Improved with plasmapheresis</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>68</td>
<td>7</td>
<td>RNS showed facial (52%) and ulnar (21%) nerve decrement</td>
<td>Anti-AChR Abs+</td>
<td>Generalized MG</td>
<td>Responsive to one cycle of intravenous immunoglobulin treatment</td>
<td></td>
</tr>
<tr>
<td>Pérez Álvarez et al., 2020 [13] Male</td>
<td>48</td>
<td>15</td>
<td>Not done</td>
<td>Anti-AChR Abs+</td>
<td>Ocular MG</td>
<td>The patient improved with hydroxychloroquine and azithromycin</td>
<td></td>
</tr>
<tr>
<td>Assini et al., 2021 [14] Male</td>
<td>77</td>
<td>56</td>
<td>RNS and SFEMG consistent with MG</td>
<td>Anti-AChR Abs--; anti-MuSK Abs+; anti-LRP4 Abs--; anti-titin Abs--;</td>
<td>Oculobulbar MG</td>
<td>Pyridostigmine (60 mg four times a day) with unsatisfactory clinical response, followed by immunosuppressive therapy (azathioprine 1.5 mg/kg/day) with an improvement in MG</td>
<td></td>
</tr>
<tr>
<td>Huber et al., 2020 [3] Female</td>
<td>21</td>
<td>10</td>
<td>Facial RNS was normal. SFEMG not performed</td>
<td>Anti-AChR Abs+; anti-MuSK Abs--; anti-LRP4 Abs--;</td>
<td>Ocular MG</td>
<td>Intravenous immunoglobulins and oral pyridostigmine.</td>
<td></td>
</tr>
<tr>
<td>Sriwastava et al., 2021 [8] Female</td>
<td>65</td>
<td>11</td>
<td>Facial RNS and SFEMG consistent with MG decremental response over more than 10% on RNS of orbicularis oculi</td>
<td>Anti-AChR Abs+; anti-MuSK Abs--;</td>
<td>Ocular MG</td>
<td>Pyridostigmine 60 mg every six hours</td>
<td></td>
</tr>
</tbody>
</table>
TABLE 2: Cases of myasthenia gravis associated with COVID-19 described in the literature.

In summary, 13 patients had anti-AChR antibodies, two patients had anti-MuSK antibodies, and one had both anti-AChR antibodies and anti-titin antibodies. The average age of diagnosis was 51.8 [19], and the average time to onset of symptoms post-COVID-19 infections was 19.9 days [5]. MG manifested as generalized muscle weakness in 10 patients, whereas three patients presented with ocular MG. Two patients had an oculobulbar presentation; one of the patients then progressed to generalized muscle weakness. Five patients initially needed at least one course of intravenous immunoglobulin (IVIg), and two patients underwent plasmapheresis. Twelve patients were treated with pyridostigmine and/or prednisone as initial therapy or after IVIg/plasmapheresis and three patients needed azathioprine in addition. All patients were reported to have improved after therapy. For one case, the therapy was not described [11]. A prospective follow-up of patients with post-COVID-19 MG will provide valuable information about their prognosis and outcomes which could provide clarity on the association between COVID-19 and other autoimmune conditions. MG may present in elderly people; however, the diagnosis can be missed because it may go unrecognized due to the comorbidities and anti-AChR and anti-MuSK antibodies being negative. This article raises awareness regarding the association between the two conditions; however, evidence from

Conclusions

To our knowledge, this is the first reported case of double-seronegative MG post-COVID-19 infection. The mechanisms for the development of MG post-COVID-19 are unknown. MG may be missed in patients after COVID-19 infections because of the comorbidities and anti-AChR and anti-MuSK antibodies being negative. This article raises awareness regarding the association between the two conditions; however, evidence from
more case series is important to analyze the pathological timeline and the immunological characteristics of COVID-19-induced MG which can prove to have morbidity and mortality benefit in patients, especially with respiratory compromise.

**Additional Information**

**Disclosures**

**Human subjects:** Consent was obtained or waived by all participants in this study. **Conflicts of interest:** In compliance with the ICMJE uniform disclosure form, all authors declare the following: **Payment/services info:** All authors have declared that no financial support was received from any organization for the submitted work. **Financial relationships:** All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. **Other relationships:** All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

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