

New-Onset Myasthenia Gravis Confirmed by Electrodiagnostic Studies After a Third Dose of SARS-CoV-2 mRNA-1273 Vaccine

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Abstract: Coronavirus disease 2019 vaccine-related pathology is a rare occurrence with few reported cases. We report on a case of a 60-yr-old man experiencing symptoms of dysphagia, dysarthria, diplopia, and weakness with onset 6 days after receiving a third full dose of SARS-CoV-2 vaccine (mRNA-1273 vaccine) in August 2021, which he received outside of the Center for Disease Control recommended guidelines, at 4 mos after his second dose of the Moderna vaccination course in March 2021. The Food and Drug Administration Emergency Use Authorization for mRNA-1273 booster was established in October 2021.

Over the next month, the patient's symptoms progressed including his inability to swallow, requiring hospitalization due to dehydration and malnutrition. Evaluation including laboratory prompted referral for electrodiagnostic studies consisting of repetitive nerve stimulation studies and needle electromyography, confirming a case of new onset bulbar myasthenia gravis.

Key Words: Myasthenia Gravis, COVID-19, SARS-CoV-2, mRNA-1273, mRNA Vaccine, Neuromuscular Disorder, Case Report

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Human coronaviruses are known to cause respiratory symptoms.¹ Research evidence has shown that severe coronavirus infections, such as those reported from COVID-19 infection, can cause not only olfactory and gustatory dysfunction cranial nerve involvement, seizures, and cerebrovascular events, but also more rare neurologic complications, such as Guillain-Barré syndrome and myasthenia gravis.

Myasthenia gravis is an autoimmune disorder in which autoantibodies are produced against the acetylcholine receptors at the neuromuscular junction.² The main resulting effects are fatigability of muscles, which can manifest focally or more generalized. Infections are known triggers of myasthenia gravis and can cause myasthenic crises.³ A myasthenic crisis is a severe and dreaded complication, which results from profound

respiratory muscle weakness; it may require intubation and mechanical ventilation.⁴ Several studies have reported exacerbation of myasthenia gravis after infection with COVID-19, with some patients requiring mechanical ventilation.⁵ There is a dearth of information regarding infections playing a causal role in the development of de novo myasthenia gravis.

Vaccines were designed to lessen morbidity and mortality associated with COVID-19 infection.⁶ Other drugs and therapies, which potentially induce new-onset myasthenia gravis, have already been described in the literature, such as the case of patients being treated with immune checkpoint inhibitors.⁷

We will review a case of new-onset bulbar myasthenia gravis that developed shortly after a patient received a third dose of the SARS-CoV-2 vaccine (mRNA-1273 vaccine), 4 mos after receipt of his second vaccine dose. This study conforms to all Case REports guidelines and reports the required information accordingly (see Supplementary Checklist, Supplemental Digital Content 1, <http://links.lww.com/PHM/B742>).

CASE PRESENTATION

A 60-yr-old male veteran, with significant medical history including hypertension, hyperlipidemia, supraventricular tachycardia, and type 2 diabetes mellitus with associated peripheral neuropathy, reported development of dysarthria 6 days after receiving a third dose of SARS-CoV-2 mRNA-1273 vaccine in August of 2021. He had received the regular series of 2 doses of SARS-CoV-2 mRNA-1273 vaccine in February and March 2021, respectively. This third dose was acquired by the patient, but not administered according to schedule as an approved booster dose. The SARS-CoV-2 mRNA-1273 vaccine was only Food and Drug Administration approved for booster dose in October 2021 with Center for Disease Control recommendation of eligibility for booster shot after 6 mos or more after completing the initial series of two shots.

Twelve days after receiving the third vaccine dose, the patient presented to the emergency department with complaints of progressively worse dysarthria and new onset of vertical diplopia that had started 6 days before. Laboratory workup at the time included urinalysis, complete blood count, basic serum chemistry panel, coagulation studies, and drug toxicology screen. These were all essentially normal. Imaging studies included a brain computed tomography scan without contrast and carotid ultrasound, which were also unremarkable and he was discharged home. Two days after emergency department discharge, the patient began to develop difficulty swallowing solid foods, followed by new right eye ptosis. One month after receiving the vaccine, he reported subjective dyspnea with conversation and complained to his primary care provider of progressive

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worsening of dysarthria, diplopia, right eye ptosis, dysphagia, and extreme fatigue of the limbs. He was treated with an oral methylprednisolone taper while awaiting outpatient neurology consultation, with partial improvement in diplopia (all other symptoms remained unchanged).

On day 39 after the third dose of vaccine, he returned to the emergency department with inability to swallow food, liquids, or oral medications; at the time, he also reported an associated 35-lb weight loss over 2–3 wks. He was admitted to the hospital for evaluation and management of dysphagia and weakness. Nasogastric tube was used for medication administration and nutrition. Although the patient reportedly developed generalized weakness and dyspnea with light exertion, he did not require supplemental oxygen during the hospitalization.

Testing results revealed unremarkable electrocardiogram and cardiac workup. Blood chemistry results showed elevated serum urea nitrogen of 41 and creatinine of 1.3. Complete blood count reported leukocytosis of 14.0. Also tested and unremarkable were a thyroid panel, thyroglobulin antibody, thyroperoxidase, calcitonin, vitamin B₁₂, and folate. Antismooth muscle immunoglobulin G was negative at less than 20 U and rapid plasma reagin screen nonreactive. His antinuclear antibody was positive with antinuclear antibody titer of 1:160 (>1:40 positivity). Coronavirus disease 2019 polymerase chain reaction testing was negative. After the electrodiagnostic study, specialized testing with acetylcholine antibody titers was collected (Supplementary Table 1, Supplemental Digital Content 2, <http://links.lww.com/PHM/B743>).

Electrodiagnostic studies consisting of repetitive nerve stimulation were completed on day 40 after third-vaccine dose. The study was clearly consistent with a postsynaptic neuromuscular junction disorder, as seen in bulbar myasthenia gravis. He displayed significant dysarthria with low voice quality and hoarseness, relying on writing for communication. Repetitive nerve stimulation study was completed on the abductor digiti minimi (ulnar) and the nasalis (facial) muscles at rest (baseline), after 1 min of muscle contraction (exercise), 1 min after exercise, 2 mins after exercise, and 3 mins after exercise. The study showed normal motor amplitudes of the left ulnar nerve compound motor action potential recording at the abductor digiti minimi. However, there was electrodiagnostic evidence of postexercise exhaustion with stimulation at the right facial nerve (recording at the nasalis muscle) with more than 10% decrement of amplitude characteristic of a postsynaptic neuromuscular junction disorder (myasthenia gravis; Fig. 1, Table 1). Needle electrode electromyography of multiple muscles (distal and proximal) of the upper and lower limbs was normal as well as testing of the masseter and tongue muscles.

The patient received treatment with pyridostigmine, reporting improvement of symptoms. An edrophonium challenge was positive. Additional computed tomography scan of the thorax showed no evidence of thymoma or other masses. The patient did not have any family history of myasthenia gravis or other autoimmune diseases.

DISCUSSION

Recent studies published throughout the ongoing SARS-CoV-2 (COVID-19) pandemic have explored COVID-19 infection and its relationship to adverse respiratory and neurological

manifestations, including myasthenia gravis.^{2,3,5} Infections are known triggers of this chronic autoimmune condition. The mechanisms that underlie this process are thought to be related to both innate and adaptive immunity, including molecular mimicry that exists between viral proteins and proteins found in peripheral nerves.^{1,8} In addition, the novel COVID-19 virus has a higher affinity for the angiotensin-converting enzyme receptor 2, which is found on neurons and endothelial cells.⁵

There is increasing evidence that infection with COVID-19 affects patients with myasthenia gravis. A small number of cases of myasthenia gravis exacerbations caused by COVID-19 infection have been described, with some patients requiring IVIG and corticosteroids and for at least two cases, with mechanical ventilation.⁹ A recent case report describes newly diagnosed ocular myasthenia gravis in a patient with no history of neuromuscular disease who initially presented with a positive nasal reverse transcription polymerase chain reaction COVID-19 test and left eye ptosis.² This patient was treated for septic shock after her initial discharge and later displayed severe respiratory symptoms probably due to SARS-CoV-2 infection, requiring 4 L of supplemental oxygen, prone positioning in the intensive care unit, along with pyridostigmine and high-dose steroids. One report published in the *Annals of Internal Medicine* described several cases of patients who were diagnosed with myasthenia gravis after acquiring infection with COVID-19. They note that the symptoms appeared 5–7 days after fever onset and that this is “consistent with time from infection to symptoms in other neurologic disorders triggered by infection.”¹⁰

Although infections are known triggers of autoimmune disorders, vaccinations are not commonly associated with myasthenia gravis. A recent case study published by Chavez and Pougner¹⁰ reported a patient who developed concerning bulbar symptoms (intermittent slurred speech) 2 days after receiving a second dose of the BNT162b2 vaccine and was diagnosed with late-onset myasthenia gravis.¹⁰ In our case, the short period between the vaccine and the onset of symptoms raises concerns about an association between myasthenia gravis and receiving a third dose of mRNA-1273 SARS-CoV-2 vaccine. Ruan et al.¹¹ found that among 22 myasthenia gravis patients who had been given inactive vaccines, two patients developed mild worsening of their symptoms within 7–20 days after vaccination.¹¹ The authors acknowledge that although infection is the most common trigger of symptom exacerbation in myasthenia gravis patients, for safety and efficacy, patients should ideally be vaccinated when their symptoms are completely stable.

Our case demonstrates myasthenia gravis confirmed by electrodiagnostic evaluation and serologic testing in a patient who had received an early third dose of the SARS-CoV-2 mRNA-1273 vaccine 6 days before the onset of symptoms. One recent case report by Tagliaferri et al.⁸ described the precipitation of a myasthenic crisis in a patient with a history of myasthenia gravis who had received the mRNA-1273 SARS-CoV-2 vaccine 1 wk earlier.⁸ Similarly, Watad et al.⁷ describes two separate cases of new onset myasthenia gravis days after the patients received a second dose of BNT162b2. General immune system stimulation (adjuvant effect) of both novel mRNA and other vaccines coupled is also biologically plausible as well as more specific cross-reactivity.⁷ In addition, Ishizuchi et al.¹² (2022) reported that among a cohort of 294 myasthenia gravis patients receiving a COVID-19 vaccine (either BNT162b2 or

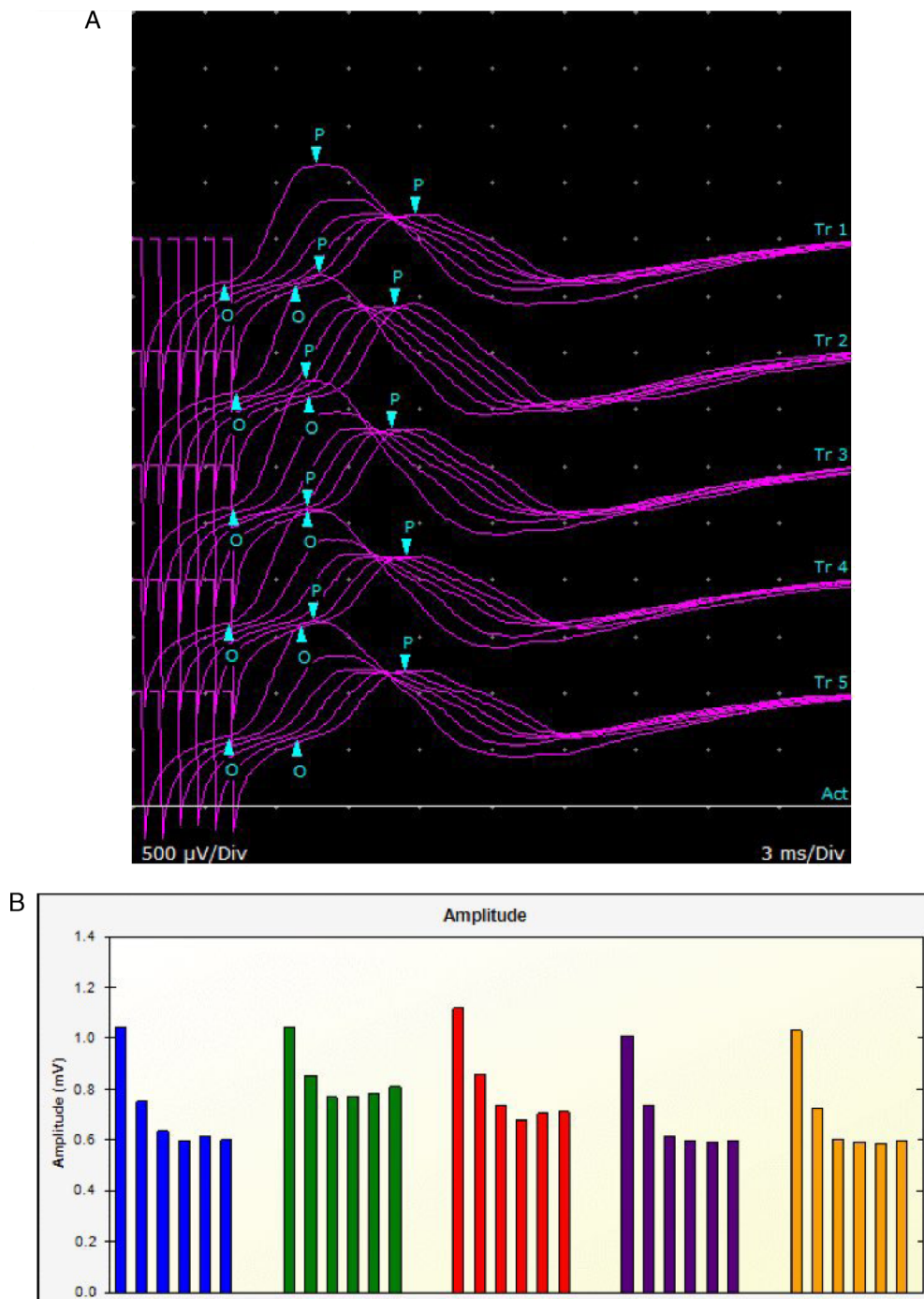


FIGURE 1. Waveforms (A) and diagram (B) generated during repetitive nerve stimulation study of the right nasalis (facial nerve). There is evidence of greater than 10% decrement of amplitude of the action potentials during repetitive nerve stimulation significant for postexercise exhaustion characteristic of myasthenia gravis.

mRNA-1273), 1.0% experienced a flare of their existing disease within 2–14 days of vaccine administration. There was no alternative explanation for the flare of their preexisting myasthenia gravis.

No previous study, to our knowledge, has described a diagnosis of myasthenia gravis in the setting of a SARS-CoV-2 vaccine booster (mRNA-1273). There is no clear causal link between the patient receiving the vaccination and the manifes-

tation of symptoms. Because of the proximity of time and no other known inciting or heritable factors, we must be suspicious of a clinical association. Most available literature focuses on the preexisting population of myasthenia gravis patients and the safety and tolerability of COVID-19 vaccination for these patients. Our case adds to the existing literature on this subject, although this does not imply causation of myasthenia gravis from receipt of an mRNA-1273 vaccine dose. Further

TABLE 1. Repetitive nerve stimulation study of the left abductor digiti minimi (top) and right nasalis muscle (bottom)

Trial #	Label	Amp 1, mV, O-P	Amp 5, mV, O-P	Amp, %, Dif	Area 1, mV·ms	Area 5, mV·ms	Area, % Dif	Rep Rate	Train Length	Pause Time, min:sec
Left abd dig minimi										
Tr 1	Baseline	7.85	7.60	-3.1	22.40	20.90	-6.7	3.00	10	00:30
Tr 2	Postexercise	8.28	8.17	-1.3	22.87	22.54	-1.5	3.00	10	01:00
Tr 3	1 min Post	8.43	8.35	-0.9	25.59	24.27	-5.2	3.00	10	01:00
Tr 4	2 mins Post	8.64	8.39	-2.8	26.71	25.04	-6.3	3.00	10	01:00
Tr 5	3 mins Post	8.63	8.41	-2.6	26.70	24.98	-6.5	3.00	10	00:00
Right nasalis										
Tr 1	Baseline	1.04	0.61	-41.2	5.57	0.00	-100.0	3.00	10	00:30
Tr 2	Postexercise	1.04	0.78	-25.2	4.67	3.73	-20.1	3.00	10	01:00
Tr 3	1 min post	1.12	0.70	-36.9	5.08	3.64	-28.4	3.00	10	01:00
Tr 4	2 mins post	1.01	0.59	-41.3	4.77	3.24	-32.0	3.00	10	01:00
Tr 5	3 mins post	1.03	0.58	-43.2	5.11	0.00	-100.0	3.00	10	00:00

The left abductor digiti minimi revealed consistent amplitudes throughout repetitive nerve stimulation study demonstrating normal activity of the ulnar nerve. The right nasalis (facial nerve) demonstrated a greater than 10% reproducible decrement of amplitude during the 5 repetitive nerve stimulation trials consistent with neuromuscular junction transmission defect.

work should be considered to elucidate possible factors, which contribute to the development of neuromuscular disease and mRNA COVID-19 vaccinations.

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