The Neurohospitalist
2023, Vol. 13(3) 303–307
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DOI: 10.1177/19418744231158161
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Myasthenia Gravis Exacerbation Following Immunization With the BNT162b2 mRNA COVID-19 Vaccine: Report of a Case and Review of the Literature

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Abstract

Acute exacerbations of Myasthenia Gravis (MG) may be triggered by infections and certain drugs. No consensus has been reached on vaccines and the risk for developing myasthenic crisis. During the COVID-19 pandemic, MG patients are considered at high risk for severe illness, and vaccination is strongly recommended. We report the case of a 70-year-old woman with MG, diagnosed 2 years earlier, that developed myasthenic crisis 10 days after the second dose of the BNT162b2 mRNA COVID-19 vaccine (Pfizer-BioNTech). The patient had no previous MG exacerbations in her history. Following increase of oral pyridostigmine and prednisone treatment, the patient underwent immunoglobulin and plasma exchange therapy. Due to persisting symptoms, immunotherapy was switched to rituximab, under which a clinical remission was achieved. MG patients infected with SARS-CoV-2 may develop severe acute respiratory distress syndrome and have a higher mortality compared to the general population. In addition, reports of new-onset MG following COVID-19 infection accumulate. By contrast, since the beginning of the vaccination program, only 3 cases of new-onset MG after COVID-19 vaccinations have been published and 2 cases of severe MG exacerbation. Vaccinations in MG patients have always been debated, but most studies confirm their safety. In the era of COVID-19 pandemic, vaccination protects against infection and severe illness, especially in vulnerable populations. The rare occurrence of side effects should not discourage clinicians from recommending COVID-19 vaccination, but close follow-up of MG patients is recommended during the post-vaccination period.

Keywords

myasthenia gravis, myasthenia crisis, acute respiratory distress syndrome COVID-19, vaccination

Introduction

Myasthenia Gravis (MG) is a rare acquired autoimmune disease of the neuromuscular junction, caused by antibodies that target the postsynaptic membrane, resulting in muscle weakness. The severity of the symptoms varies from ocular manifestations with diplopia and ptosis, to a more generalized form, involving limb, axial and bulbar muscles and finally respiratory muscles, resulting in respiratory failure and need for intensive care support.

Acute exacerbations of MG, requiring intubation or noninvasive ventilation, may occur during the course of the disease and might have fatal outcome. One fifth of patients with MG are expected to experience an MG crisis at least once in their lives. The causes of MG exacerbations are not fully understood but can be triggered by infections, mostly bronchopulmonary, and certain drugs. No consensus has yet been reached regarding the safety of SARS-CoV-2 vaccination in MG patients.

Influenza vaccines have been assessed for their safety in MG patients systematically. Zinman et al used population-based healthcare data over a 14-year period and did not find any association between influenza vaccination and MG exacerbations needing hospitalization.[1] In another report, Auriel et al studied 74 MG patients that received the seasonal influenza and the H1N1 virus vaccine during the winter of 2009-2010.[2] None of the vaccinated patients reported any

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side effect. In a more recent paper published in 2017, researchers investigated the impact of influenza infection and vaccination on symptom severity in 258 MG patients. Myasthenic symptoms were aggravated in 40% of patients who had experienced influenza-like illness, but only in 1.5% of patients who received influenza vaccination. The authors concluded that influenza vaccination is safe and furthermore protects MG patients from severe exacerbations due to infection.[3] Gummi et al performed a retrospective chart review of patients diagnosed with MG in a single academic medical center between 2011 and 2016.[4] No adverse effects or exacerbations were reported as a result of vaccines. On the contrary, infections were among the most common factors associated with MG exacerbation. Two double-blind randomized placebo-controlled studies were published recently (2018, 2019), investigating serological and clinical course of MG after a seasonal influenza vaccination. Tackenberg et al enrolled 62 patients. Adverse effects were comparable between groups (placebo and vaccinated). No severe MG exacerbation was reported related to vaccination, nor anti–acetylcholine receptor (AChR) antibody (Ab) elevation was detected.[5] Similarly, Strijbos and colleagues enrolled 47 MG patients, and examined them 4 weeks after vaccination. Neither clinical exacerbation nor elevation of disease specific AchR-Ab were noted and concluded that influenza vaccination is safe.[6] Only a very recent paper reports a single case report of a new onset laryngeal MG following influenza vaccination.[7]

During the current COVID-19 pandemic, MG patients were considered as being at high risk for severe illness. General Guidelines by the Centers for Disease Control (CDC) advice that most MG patients should be vaccinated with any FDA-authorized COVID-19 vaccine.

Consistent with the above, we have strongly recommended vaccination of all MG patients followed up in our department. Among all patients, we encountered 1 single case of MG exacerbation, following vaccination. The patient gave informed consent for publication. This study followed the principles of the Helsinki Declaration and its later amendments.

Case Description

A middle-aged woman had been diagnosed with MG 2 years earlier, shortly after a surgery for diverticulitis. She did not have any past medical history. She developed ptosis, diplopia, nasal speaking and difficulty in swallowing. MG diagnosis was based on positive AchR-Ab and positive findings of Repetitive Nerve Stimulation on trapezoid and oriculis oculi muscles. Chest computed tomography (CT) was negative for thymoma or thymus hyperplasia. She was started on pyridostigmine 60 mg q.6 hours and prednisolone 30 mg/d. She responded to medication with almost complete alleviation of her symptoms. Six months later, she underwent a second surgery for closure of the colostomy. The operation was uneventful, the scar healed easily and soon afterwards she was started on Mycophenolate Mofetil and steroid treatment was tapered to 10 mg every other day. Almost 2 years after MG diagnosis, she underwent a right knee arthroplasty due to chronic osteoarthritis. Again, the operation was uneventful, no exacerbation of myasthenic symptoms was observed, and she was discharged from hospital starting rehabilitation at home.

On April 2021, she completed vaccination with the BNT162b2 mRNA Covid-19 (Pfizer-BioNTech) vaccine. Gradually, 10 days after the second dose, she developed ptosis, diplopia and nasal speech, and diagnosis of MG exacerbation was made on clinical grounds. Pyridostigmine and prednisolone were increased and her symptoms were alleviated temporarily. One week after remission, however, she experienced a severe clinical deterioration and was intubated because of severe respiratory distress. SARS-CoV-2 testing was negative and she did not have elevation of AChR antibodies Despite full dosage of IVIG (.4 g/kg/d over 5 days) no improvement was observed and plasma exchange was initiated. After 5 sessions of PE, she was stabilized, but had still not returned to the pre-vaccination baseline status. For that reason, considering MG was refractory to conventional treatments, she was started on rituximab and since then, MG has begun to remit, almost 4 months after vaccination.

Discussion

MG exacerbation following COVID-19 with various outcomes, have been reported. In some cases, intubation and rescue therapy were required and in others the outcome was favorable. MG patients infected with SARS-CoV-2, commonly develop severe acute respiratory distress syndrome requiring intubation and have a higher mortality compared to the general population ranging from1% to 40%. In a recent study, it was shown that, when MG patients were infected by SARS-CoV-2, 40% of them developed MG exacerbation or even crisis, requiring rescue therapy (IVIG or Plasma exchange), and a significant percentage (24%) died.[8] In an observational study, 93 MG patients were evaluated after COVID-19 infection. Exacerbation of MG during infection occurred in 35 patients and 10 deaths were recorded (11%).[9] In another multicenter, retrospective, observational cohort study including 3558 patients with MG, only 34 patients were infected with COVID-19 and 5 died.[10] Until now, several case reports of new-onset MG following COVID-19 have been published.

Before the development of vaccines against COVID-19, guidance for the management of MG during the pandemic was limited to practicing extra-vigilant social distancing to the point of avoiding any physical interaction, even medical consultation. The increased risk for severe COVID-19 and the lack of safe and effective treatment options, has led the

Table 1. Studies reporting MG exacerbation / death or new onset MG after COVID 19 infection or COVID vaccine.

Studies	Type Of Study	N	Exposure	Exacerbation of MG	Deaths	New Onset MG	Conclusion
Muppidi et al 2020[8]	Observational	91	COVID 19 INFECTION	36 pts (40%)	22pts (24%)		Patients with myasthenia gravis have a higher mortality and morbidity than the general population with COVID-19
Jakubíková et al 2021[9]	Observational	93	COVID 19 INFECTION	35 pts (38%)	10 pts (11%)		Older age, low FVC, immunosuppressive treatment predict severity of COVID-19 in MG patients
Sole et al 2021[10]	Multicenter, retrospective, observational	3558	COVID 19 INFECTION	28 pts (.9%)	5pts (1%)		MGFA class ≥ IV is associated with severe COVID-19
Watad et al 2021[11]	Observational	NA	COVID VACCINE			2 pts	Immune-mediated diseases temporally-associated with SARS-CoV-2 vaccination appear rare are moderate in severity and responsive to therapy
Chavez and Pougnier 2021[12]	Case report	1	COVID VACCINE			1 pt	New onset MG associated with COVID-19 vaccination is rare. Early recognition can lead to timely treatment
Ruan et al 2021[13]	Observational	22	COVID VACCINE	2pts (9.1%)			Inactivated COVID-19 vaccines might be safe in MG patients with MGFA class I or II
Ishizuchi et al 2022[14]	Prospective	343	COVID VACCINE	3 pts (1%)			The relative risk of COVID-19 vaccines is exceedingly low, preferentially observed in younger patients with a variety of disease classifications, autoantibody statuses and onset timing
Tagliaferri et al 2021[15]	Case report	1	COVID VACCINE	1			The risk of contracting SARS-CoV-2 infection and its Consequences outweigh the risk of adverse events from vaccination.
Sonigra et al 2022[16]	Case report	1	COVID VACCINE		1		Induction of a myasthenic crisis by the COVID-19 vaccine seems to be underreported. Enhanced monitoring of MG patients after vaccination, is recommended

Abbreviations. N: Number of patients, MG: Myasthenia Gravis, pt(s): patient (s), FVC: Forced Vital Capacity.

Centers for Disease Control and Prevention (CDC) to strongly recommend vaccination against COVID-19.

Regarding COVID-19 vaccination and MG exacerbation, published data continue to accrue. Watad et al identified 10 cases of new-onset and 17 cases of exacerbations of immune-mediated diseases following COVID-19 vaccination. Among them, 2 new-onset MG cases were included, both after the second dose of the BNT162b2 vaccine, 1 being severe and needing intubation, while the other responded to therapy and recovered quickly.[11] Similarly, another case of new-onset MG

has been reported 4 weeks after the first dose with subsequent MG exacerbation 2 days after the second dose of BNT162b2 vaccine, presenting with predominantly bulbar symptoms that progressed to generalized myasthenia requiring ventilator support.[12]

Two studies have systematically investigated safety of COVID-19 vaccines in MG patients, and none reported any fatal event or crisis. In Ruan et al study, twenty-one patients were administrated with inactivated vaccines, and 1 was administrated with recombinant subunit vaccine. Only 2 patients (9.1%) reported slight symptom deterioration, not requiring rescue therapy or intubation, within 4 weeks after vaccination.[13] Ishizuchi et al, followed 343 MG patients for 6 months, 294 of whom received COVID-19 vaccine. No fatal event was reported. Only 3 patients (1%) experienced MG deterioration, but none required intubation nor intensive care admittance.[14]

There are only 2 single case reports described severe MG deterioration attributed to COVID-19 vaccine. Tagliaferi and colleagues have described MG exacerbation 1 week after second dose of the mRNA-1273 vaccine (Moderna). The patient responded initially to IVIG but 6 days after admission he deteriorated developing respiratory failure and was intubated. The final outcome is not described.[15] Sonigra and colleagues,[16] published a similar case of severe myasthenic crisis after receiving the first dose of the ChAdOx1-S recombinant vaccine (AstraZeneca). In their reported case the patient finally succumbed.

However, in the present case, as well as in the aforementioned previously published similar cases (Table 1), although the exacerbation was temporally related to the vaccination, there is no proof of causation and it could have been coincidence.

Though MG is a rare disease, the high morbidity and mortality in the contest of COVID-19 infection demands increased awareness of best practices. The rare occurrence of adverse effects of COVID-19 vaccines should not discourage patients and, more importantly, not restrain neurologists from advising MG patients for vaccination.

Reporting cases that describe adverse effects of COVID-19 vaccines, will help identify their true incidence. More evidence is warranted to determine the critical time-period following vaccination when close monitoring and vigilance are required to identify and manage promptly potential exacerbations in MG patients.

Author Contributions

MP, GT contributed to conception and study design. MP, MIS, LP contributed to drafting a significant portion of the manuscript. GT contributed with critical comments during manuscript revision.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

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