Open Journal of
Clinical & Medical
Case Reports

Volume 9 (2023)
Issue 30

Case Report ISSN: 2379-1039

New late-onset myasthenia gravis following mRNA COVID-19 vaccination: Case report and literature review

Eser Bulus*; Selen Ucem; Gulshan Yunisova; Piraye Oflazer

***Corresponding Author: Eser Bulus**
Koç University Hospital, Department of Neurology, Istanbul, Turkey.
Email: ebulus2004@hotmail.com

Abstract

Introduction: Myasthenia gravis (MG) is a rare autoimmune disorder of the neuromuscular junction associated with post-synaptic skeletal muscle membrane protein autoantibodies against the nicotinic acetylcholine receptors (ACh-R), muscle-specific kinase (MuSK) or agrin and lipoprotein receptor-related protein 4 (LRP4). The disease pathomechanism is complex, with predisposing human leukocyte antigen genes, pro-inflammatory cytokine profile, sex hormones, pharmacological agents, and environmental triggers. Several case reports suggest SARS-CoV-2 infection and Covid-19 vaccines as a possible trigger of MG.

Case Report: We present a 69-year-old previously healthy man developing ocular and facial muscle weakness three days following the second dose of BNT162B2 vaccine. The clinical signs, decremental response on repetitive nerve stimulation (RNS) and positive anti-acetylcholine receptor antibodies (anti-AChR atb) were consistent with a diagnosis of acetylcholine receptor antibody-associated late onset MG. Pyridostigmine, intravenous immunoglobulin, oral steroid, and mycophenolate administration achieved pharmacological remission.

Conclusion: A literature review revealed four similar cases suggesting a possible association between late-onset MG and mRNA-BNT161B2 and mRNA-1273 vaccines. Although this clinical association does not impact the vaccine-related decision making, clinicians should be aware of the possibility of new onset MG following COVID-19 mRNA vaccination in the elderly population.

Keywords: COVID-19; Vaccination; Myasthenia gravis; Autoimmunity; Neuromuscular disease.

Introduction

Myasthenia gravis (MG) is a rare autoimmune disorder of the neuromuscular junction associated with post-synaptic skeletal muscle membrane protein autoantibodies, most commonly (80%) against the nicotinic acetylcholine receptors (ACh-R) [1]. Other antibodies against muscle-specific kinase (MuSK) or other neuromuscular junction proteins such as agrin and lipoprotein receptor-related protein 4 (LRP4) can be detected [2,3]. The clinical features include muscle fatigue in ocular, facial, bulbar, respiratory, limb, and truncal muscles. MG can be classified based on the age of onset, involved muscles, and laboratory findings [4]. Late-onset myasthenia gravis (LOMG) is defined when the symptoms appear at ≥50 years of age and is more common in males. [5]

Table 1: Characteristics of the reported myasthenia gravis cases following COVID-19 vaccination (N/S: not specified).

Vaccination Type	Time from vaccination to symptom onset	Demographics (Age, Sex)	Pertinent Existing Diagnosis	Presenting symptom	Anti-AChR-antibody serology	Thymoma	Treatment	Course on follow-up	Reference
mRNA-BNT162b	Three days following second dose	69, Male	(-)	Left eye droop, inability to close mouth	Elevated	(-)	Pyridostigmine + IVIg +Oral steroids+ mycophenolate	Remission	Present case
mRNA-BNT162b	Two days following second dose	82, Male	Chronic Kidney Disease	Slurred speech	Elevated	(-)	Pyridostigmine	Recurrence in 2 months	[9]
mRNA-BNT162b	One day following second dose	72, Male	Recurrent pericarditis	Moderate onset	N/S	N/S	Plasma exchange+ Oral steroids	Rapid Remission	[13]
mRNA-BNT162b	Seven days following second dose	73, Male	(-)	Severe ocular and bulber, respiratory	N/S	N/S	Oral steroids + Pyridostigmine + Plasma exchange	Intubation and ICU management	[13]
mRNA-BNT162b	<24 hours	33, Female	(-)	Bilateral eye droop, binocular diplopia	Negative	Mild thymic hyperplasia	Oral pyridostigmine 360 mg/day	Remission	[15]
mRNA-1273	One week following second dose	77, Male	Myasthenia Gravis	Dysphagia	N/S	(-)	Oral steroids+ Pyridostigmine+ IVIg	Acute Kidney Failure due to inadequate oral intake, managed in ICU	[10]

The disease pathomechanism is complex, with predisposing human leukocyte antigen genes, pro-inflammatory cytokine profile, sex hormones, pharmacological agents, and environmental triggers [1]. Identified viral triggers include, but are not limited to, Epstein-Barr virus, measles, herpesviruses, hepatitis B virus, and Zika virus. Several case reports also suggest SARS-CoV-2 infection as a possible trigger of MG [6]. An etiological association can be explained by a dysregulated toll-like receptor response to virus-associated molecular patterns in the thymus followed by overexpression of ACh-R and autosensitization, although overt manifestation of a subclinical disease due to infection is equally plausible [7]. Furthermore, trivalent influenza, hepatitis B, nine-valent human papillomavirus, BCG, and Covid-19 vaccines have been associated with new-onset MG [8-10]. Herein, we report a case of new-onset MG following mRNA BNT162B2 vaccination and outline reported cases of COVID-19 vaccine-associated new-onset MG in the literature.

Case Presentation

A 69-year-old male developed left eyelid droop and an inability to close his mouth three days following the second dose mRNA BNT162B2 vaccination. Five days later, he presented to the emergency department with difficulty rising from the chair, climbing stairs, lifting his arms, left eyelid droop and inability to close his mouth. He had a history of benign prostatic hyperplasia and contrast agent allergy. His vital signs were normal. On neurological examination left ptosis with bilateral mild weakness of eye closure was evident. Masseter muscles were weak bilaterally, causing an open-mouth appearance. Tongue muscle strength was prominently diminished, visualized by an inability to pass beyond the commissures. Muscle strength was 3/5 at neck flexors, 4-/5 at bilateral deltoideus, 4/5 at bilateral iliopsoas and extensor hallucis longus. Deep tendon reflexes were globally normoactive and pathological reflexes were absent. Cerebellar examination was normal. Speech was slightly nasal. He was admitted for inpatient investigations and management for myasthenia gravis.

Repetitive nerve stimulation (NCV) with 2 Hz and 3 Hz stimulation revealed significant decrement, an amplitude and area alteration at the right accessory and right facial nerves, which were consistent with a postsynaptic neuromuscular junction disorder. Initial laboratory tests revealed elevated creatinine kinase of 385 U/L (normal limit 200 U/L). Patient ptosis, deltoid, iliopsoas and masseter muscle weakness improved fully in one hour after oral 60 mg pyridostigmine bromide administration. In addition, dysarthria and neck flexor weakness showed significant improvement. Anti-Ach-R antibody titer was 309 nmol/L (normal <0.25 nmol/L), confirming the diagnosis of generalized late-onset myasthenia gravis. Thorax computed tomography ruled out a thymoma. A 5-day regimen of 0.4 gr/kg/day intravenous immunoglobulin (IVIg) together with oral 60 mg pyridostigmine bromide four times daily. Following complete symptom resolution under symptomatic treatment with IVIg, the patient was discharged with a prescription of 10 mg/day prednisolone in addition to continuing pyridostigmine bromide treatment. On 3-week and 3-month follow-up, the patient was asymptomatic under pyridostigmine and 10 mg/day prednisolone treatment with normal neurological examination except a mild neck flexor weakness (4/5). The prednisolone dose was reduced to 5 mg/day in the 12th month of follow-up. At the 15th month follow-up, it was learned that the patient started to have difficulty while breathing, swallowing and in keeping his neck upright position for 1 week. Muscle strength in cranial area and extremities got worsened in neurological examination. Patient was hospitalized again with the diagnosis of myasthenic crisis with bulbar involvement and 0.4 g/kg/day IVIg was administered for 5 days with pyridostigmine bromide treatment. He was discharged with prednisolone 15 mg/day and pyridostigmine bromide 60 mg five times daily treatments with clinical improvement. After one month due to the presence of fluctuating bulbar findings in the examination, 0.4 g/kg/day IVIg booster was administered and mycophenolate was added to treatment. Patient is being followed up under prednisolone 15 mg/day, pyridostigmine bromide, monthly 0.4 g/kg/day IVIg booster and mycophenolate 2000 mg/day treatments.

Discussion

The mRNA-BNT162b2 vaccine is a highly efficacious and safe tool to establish immunity against

SARS-CoV-2 [11]. The immune-related adverse events following vaccination in patients with no previous history of autoimmune disease include myocarditis [12], pericarditis [13], acute pancreatitis [14], polymyalgia rheumatica, and multiple sclerosis [13]. In addition, five cases of new-onset myasthenia gravis have been reported following BNT162b2 [9,13]. Table 1 summarizes the current reports of COVID-19 vaccination associated MG cases in the literature. Five of these cases including our case are late-onset, male and experienced the first symptom in the first week following the second dose administration of an mRNA vaccine. Only one of them was a female patient diagnosed with early-onset MG following BNT162b2 vaccine [15].

There is a COVID-19 infection associated with a MG exacerbation in the literature [16]. In a cohort of patients with pre-existing diagnosis of MG, inactivated or recombinant subunit COVID-19 vaccination did not lead to symptom exacerbation [17], however a dysphagia episode following mRNA-1273 vaccine in an MG patient has been reported [10]. In light of these reports, new-onset MG cases can be explained by a latent MG becoming clinically apparent following mRNA vaccination. Alternative hypotheses explaining such occurrences are molecular mimicry, bystander effect, and epitope spreading [18]. Finally, the possible activation of ACh-R by SARS-CoV-2 spike protein has been suggested to have a pro-inflammatory role in COVID-19 [19]. Whether this association can be linked with ACh-R antibody formation in patients with COVID-19 infection or vaccination requires further investigation.

Conclusion

The occurrence of new-onset MG following COVID-19 mRNA vaccination should not impact any vaccine administration practices; however, the alterations in humoral and adaptive immune responses following mRNA vaccination, especially in elderly populations should be investigated.

References

1. Gilhus NE, Tzartos S, Evoli A, Palace J, Burns TM, Verschuuren JJGM. Myasthenia gravis. Nature Reviews Disease Primers. 2019; 58: 30.

2. Hoch W, McConville J, Helms S, Newsom-Davis J, Melms A, Vincent A. Auto-antibodies to the receptor tyrosine kinase MuSK in patients with myasthenia gravis without acetylcholine receptor antibodies. Nat Med. 2001; 7: 365-8.

3. Richman DP. The Future of Research in Myasthenia. JAMA Neurol. 2015; 72: 812-4.

4. Jayam Trouth A, Dabi A, Solieman N, Kurukumbi M, Kalyanam J. Myasthenia gravis: A review. Autoimmune Dis. 2012; 2012: 874680.

5. Aarli JA. Late-onset myasthenia gravis: A changing scene. Arch Neurol. 1999; 56: 25-7.

6. Karimi N, Okhovat AA, Ziaadini B, Haghi Ashtiani B, Nafissi S, et al. Myasthenia gravis associated with novel coronavirus 2019 infection: A report of three cases. Clin Neurol Neurosurg. 2021; 208: 106834.

7. Cavalcante P, Cufi P, Mantegazza R, Berrih-Aknin S, Bernasconi P, et al. Etiology of myasthenia gravis: Innate immunity signature in pathological thymus. Autoimmun Rev. 2013; 12: 863-74.

8. Wang F, Xiang T, He L, Wang J. Laryngeal myasthenia gravis following influenza vaccination: A case report and literature review. Hum Vaccin Immunother. 2021; 17: 5539-5531.

9. Chavez A, Pougnier C. A Case of COVID-19 Vaccine Associated New Diagnosis Myasthenia Gravis. Journal of Primary Care & Community Health. 2021; 12: 21501327211051933.

10. Tagliaferri AR, Narvaneni S, Azzam MH, Grist W. A Case of COVID-19 Vaccine Causing a Myasthenia Gravis Crisis. Cureus. 2021; 13: e15581.

11. Polack FP, Thomas SJ, Kitchin N, Absalon J, Gurtman A, et al. Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine. New England Journal of Medicine. 2020; 383: 2603-2615.

12. Bozkurt B, Kamat I, Hotez PJ. Myocarditis With COVID-19 mRNA Vaccines. Circulation. 2021; 144: 471-484.

13. Watad A, De Marco G, Mahajna H, Druyan A, Eltity M, et al. Immune-Mediated Disease Flares or New-Onset Disease in 27 Subjects Following mRNA/DNA SARS-CoV-2 Vaccination. Vaccines (Basel). 2021; 9: 435.

14. Parkash O, Sharko A, Farooqi A, Ying GW, Sura P. Acute Pancreatitis: A Possible Side Effect of COVID-19 Vaccine. Cureus. 2021; 13: e14741.

15. Lee MA, Lee C, Park JH, Lee JH. Early-Onset Myasthenia Gravis Following COVID-19 Vaccination. J Korean Med Sci. 2022; 37: e50.

16. Singh S, Govindarajan R. COVID-19 and generalized Myasthenia Gravis exacerbation: A case report. Clin Neurol Neurosurg. 2020; 196: 106045.

17. Ruan Z, Tang Y, Li C, Sun C, Zhu Y, Li Z et al. COVID-19 Vaccination in Patients with Myasthenia Gravis: A Single-Center Case Series. Vaccines (Basel). 2021; 9: 1112.

18. Zhou Q, Zhou R, Yang H, Yang H. To Be or Not To Be Vaccinated: That Is a Question in Myasthenia Gravis. Front Immunol. 2021; 12: 733418.

19. Alexandris N, Lagoumintzis G, Chasapis CT, Leonidas DD, Papadopoulos GE, et al. Nicotinic cholinergic system and COVID-19: In silico evaluation of nicotinic acetylcholine receptor agonists as potential therapeutic interventions. Toxicology Reports. 2020; 8: 73-83.

Manuscript Information: Received: July 23, 2023; Accepted: September 05, 2023; Published: September 08, 2023

Authors Information: Eser Bulus[1]*; Selen Ucem[2]; Gulshan Yunisova[1]; Piraye Oflazer[1,2]

[1]Koç University Hospital, Department of Neurology, Istanbul, Turkey.

[2]Koç University School of Medicine, Department of Neurology, Istanbul, Turkey.

Citation: Bulus E, Ucem S, Yunisova G, Oflazer P. New late-onset myasthenia gravis following mRNA COVID-19 vaccination: Case report and literature review. Open J Clin Med Case Rep. 2023; 2108.