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COVID-19

New-onset myasthenia gravis after mRNA SARS-CoV-2 vaccination: a case series

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Abstract

Background Myasthenia gravis (MG) is an autoimmune disease that targets acetylcholine receptor (AChR) of the neuromuscular junction. New-onset MG after SARS-CoV-2 vaccination has rarely been reported.

Case presentation We report about three patients who presented new-onset myasthenia gravis after receiving mRNA SARS-CoV-2 vaccination. The patients were all males and older than 55 years. All the patients presented with ocular and bulbar symptoms. The interval between vaccine administration and MG onset ranged from 3 days after the first dose to 10 days after the second dose. All the patients had elevated serum AChR antibodies and responded to pyridostigmine. Two out of three patients were successfully treated with IVIG or plasma exchange and with long-term immunosuppression.

Conclusions MG is a rare disease; clinicians should be aware of possible new-onset MG after SARS-CoV-2 vaccination, especially with the current recommendation of booster doses. The hyperstimulation of the innate immune system or the exacerbation of a subclinical pre-existing MG could be possible explanations.

Keywords Myasthenia gravis · COVID-19 · SARS-CoV-2 · Vaccine · mRNA

Introduction

Myasthenia gravis (MG) is an autoimmune disease that targets acetylcholine receptor (AChR) in postsynaptic membrane of the neuromuscular junction or its functionally related components and is characterized by fatigable muscle weakness.

Rarely, MG onset can be triggered or worsened by infectious diseases [1] but this topic is still a matter of debate [2]. Vaccination as a possible trigger for MG has rarely been described [3, 4].

The role of SARS-CoV-2 infection as a trigger of autoimmune diseases is being recognized [5] and a few cases of MG associated with SARS-CoV-2 infection have been described [6–9].

The COVID-19 vaccination has been described as the cause of myasthenic crisis in two already diagnosed MG patients [10, 11] and as a trigger of other immune-mediated disorders [12]. New-onset MG after SARS-CoV-2 vaccination has rarely been reported [12, 13].

Herein, we describe three patients who were diagnosed with new-onset MG, after mRNA SARS-CoV-2 vaccination.

Case reports

The main features of the three patients are summarized in Table 1.

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Table 1 Summary of the three patients' clinical findings

	Patient 1	Patient 2	Patient 3
Age (years)	91	80	55
Gender	M	M	M
Onset from vaccination	10 days after the second dose	6 days after the second dose	3 days after the first dose; worsened after the second dose
Muscle fatigability	Yes	Yes	Yes
MG type	Oculobulbar	Oculobulbar	Generalized
RNS	Decremental response (−58%) at 3 Hz stimulation	Decremental response (−49%) at 3 Hz stimulation	Decremental response (−51%) at 3 Hz stimulation
AChR-Ab (nmol/L)	10.50	9.00	6.10
Chest CT: thymic residuals or thymoma	No	No	No
Thyroid function and thyroid Ab	TSH 0.616 uU/mL	TSH 3.630 uU/mL	TSH 1020 uU/mL negative thyroid Ab

Patient 1

A 90-year-old male with chronic ischemic heart disease and chronic kidney disease in solitary kidney progressively developed intense asthenia and fatigability, head drop, and bilateral ptosis. He first underwent cardiologic examination and heart ultrasound (US) that were both unremarkable. Since the symptoms worsened, he was referred to the neurology department. He showed bilateral but asymmetrical ptosis, horizontal diplopia, and limitation in the upward gaze, and neck extensor muscle strength was 2/5 on the Medical Research Council (MRC) scale, neck flexor muscle strength was 3/5 on the MRC scale causing head drop, and proximal upper and lower limb strength was 4/5 on the MRC scale and showed fatigability after prolonged contraction. The symptoms started 10 days after the second dose of BNT162b2; the first dose was given 3 weeks earlier without any significant side effect. Repetitive nerve stimulation (RNS) of the facial nerve was consistent with a postsynaptic neuromuscular junction disorder. Serum AChR antibody titer was 10.50 nmol/L. Chest computed tomography (CT) was negative for thymic changes. PET-CT scan of the body excluded occult malignancies. Thyroid US showed multinodular struma; serum TSH was 0.616 uU/ml. A diagnosis of MG was made on the basis of the clinical and instrumental features. Pyridostigmine at the dosage of 30 mg three times per day was able to control the symptoms and, due to the patient's age and comorbidities, we decided not to start any additional immunosuppressive treatment. At 1 month following discharge, myasthenic symptoms were unchanged.

Patient 2

An 80-year-old male with hypertension, type II diabetes mellitus, and hypercholesterolemia presented to the neurology department with new onset of bilateral ptosis, diplopia, dysphagia, and head drop. The neurological examination showed a complete ptosis in the right eye, partial ptosis in the left eye, diplopia in all directions of gaze, dysphonia, orbicularis oculi, and tongue weakness (3/5 MRC both) and head drop (neck flexor muscle strength 3/5 MRC, neck extensor muscle strength 2/5 MRC). Fatigability was detectable in all these muscles, while limb muscles were unaffected. His ptosis temporarily improved with ice pack test. The symptoms had started 6 days after the injection of the second dose of mRNA-1273; the first dose was given 4 weeks earlier and the only side effect was pain in the injection site. RNS of the facial nerve was consistent with a postsynaptic neuromuscular junction disorder. Serum AChR antibody titer was 9.00 nmol/L. Chest CT was negative for thymic changes. Serum TSH was 3.630 uU/ml. Pyridostigmine 30 mg three times daily and prednisone 25 mg daily were started, but the clinical conditions of the patient continued to worsen and he was given five plasma exchange sessions (30 mL of plasma/kg body weight per session). From the second session, a clinical improvement was seen. Considering the high metabolic risk of the patient, a steroid-sparing immunosuppressive treatment was chosen and azathioprine was started at 25 mg daily and weekly titrated up to 150 mg daily. At hospital discharge, his neurologic examination was normal apart from a mild ptosis of the right eyelid after 15 s on sustained upward gaze. At 3 months following discharge, the patient had residual mild ptosis in the right eye, and no signs of bulbar or spinal fatigability; serum AChR antibody titer was reassessed and was 7.7 nmol/L.

Patient 3

A 55-year-old male with hypertension and chronic tension-type headache presented to the emergency department for

weakness and fatigability in the upper limb as well as in the neck muscles and fluctuating diplopia. He also complained neck pain and orthopnea. His neurological examination showed horizontal diplopia on left and right lateral gaze, muscular weakness, and fatigability of the neck flexor muscles (3/5 MRC) and of the proximal muscles of both the upper (2/5 MRC) and, to a much lesser degree, the lower limbs (4/5 MRC). The symptoms had started about 2 months earlier, 3 days after the first dose of mRNA-1273 injection, but significantly worsened after 4 weeks when the second dose was administered.

RNS of the left facial and the spinal accessory nerve were consistent with a postsynaptic neuromuscular junction disorder. Serum AChR antibody titer was 6.10 nmol/L. Chest CT was negative for thymic changes. TSH was 1020 uU/mL. Clinical conditions and muscular fatigability improved with pyridostigmine 60 mg 4 times/daily and after a 5 days' IVIG course (total dosage of 150 g).

When the patient was discharged, the neurological examination showed ptosis in the left eye after 50 s on sustained upward gaze, and bulbar and spinal muscle strength was normal with no signs of fatigability. The treatment schedule at discharge included pyridostigmine and prednisone 50 mg daily. At 3 months following discharge, the patient showed mild upper limb fatigability after 90 s on sustained abduction of the arms, and no signs of bulbar and ocular involvement were detected.

Discussion

Cumulative evidence are pointing out that SARS-CoV-2 may play a role as a trigger of autoimmunity through two different mechanisms: firstly by inducing hyperstimulation of the innate immune system and secondly by molecular mimicry between components of SARS-CoV-2 and self-components of the host [5]. Several cases of new-onset immune-mediated diseases among patients with SARS-CoV-2 infection have been described [14, 15].

To date, eight cases of new-onset MG after SARS-CoV-2 infection have been reported in the literature [6–9]. Six out of eight patients were aged above 50 years. The majority of patients had mild symptomatic COVID-19. The mean interval between COVID-19 and MG onset was 3 weeks.

As opposed to immune-mediated diseases associated with SARS-CoV-2 infection, new-onset immune-mediated disorders after vaccination are rare. Only three cases of new-onset MG after SARS-CoV-2 vaccination were reported so far in the literature [13, 16]. In addition, only two cases of myasthenic crisis in already diagnosed MG patients have been described [10, 11] and another study showed no worsening symptoms after inactivated or recombinant SARS-CoV-2 vaccination in MG patients, except for two patients with slight symptom worsening that quickly resolved within a few days [17].

Considering our three cases, all six patients with new-onset MG after SARS-CoV-2 vaccination were males and were all aged above 55 years. All six patients received a mRNA vaccination and four out of six patients developed MG symptoms after the second dose, and two patients developed symptoms after the first dose and worsened after the second dose [13].

mRNA vaccines elicit immunity though the intrinsic immunostimulatory properties of RNA that serves as both immunogen and adjuvant. RNAs are recognized by Toll-like receptors (TLR), namely TLR3, 7, 8, and 9, as well as several components of the inflammasome. The final result is the activation of pro-inflammatory cascades and production of cytokines. The upregulation of these immunological pathways seems to be implicated in numerous inflammatory/autoimmune disease, among which we can find MG [18, 19]. Indeed, a possible mechanism through which mRNA vaccine might induce an immune-mediated disease is bystander activation; i.e., hyperstimulation of the innate immune system, as part of the vaccine response, causes cytokine production and release of previously existing self-antigens, resulting in the activation of autoreactive T cells [20].

On the other hand, another plausible mechanism could be that vaccination has been a trigger of an already existing but asymptomatic form of MG, since we did not know the preceding antibody status of our patients. Moreover, animal models of MG have shown that rapid onset of myasthenic symptoms within 24–48 h occurs only with passive transfer of antibodies [21], while the injection of antigen to elicit an active immune response takes a much longer time (over 14 days) to develop myasthenic symptoms [22]. Therefore, all our patients could have been affected by a subclinical pre-existing form of MG, especially our third case, in which myasthenic symptoms developed as early as 3 days after the first dose.

Lastly, another potential mechanism could be molecular mimicry between the spike protein of SARS-CoV-2 and hosts self-antigens. Antibodies against SARS-CoV-2 spike have been experimentally shown to cross-react with structurally similar human peptide protein sequences, including actin and alpha-myosin [23]. Moreover, an interaction between SARS-CoV-2 spike and α7 nicotinic AChR has been suggested [24]. However, α7 nicotinic AChR is expressed in the peripheral nervous system, dorsal root ganglia, and parasympathetic and sympathetic ganglia but not expressed in the striated muscle [25]. Therefore, a molecular mimicry between AChR and SARS-CoV-2 spike protein has not been proven.

This case series highlights the importance of recognizing rare immune-mediated disorders temporally related to SARS-CoV-2 vaccination. Whether the vaccine is causally

related to the development of MG or a random occurrence is not clear and supporting evidences on a causal relationship are scarce. It is conceivable that the vaccine might have triggered an immune-mediated process in predisposed subjects or most likely exacerbated a subclinical pre-existing form of MG.

Declarations

Ethical approval None.

Informed consent Informed consent was obtained from the patients included in this study.

Conflict of interest The authors declare no competing interests.

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