The Clinical Course of New-Onset Ocular Myasthenia Gravis Caused by Pfizer–BioNTech COVID-19 Vaccine

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Abstract

Purpose: Myasthenia gravis (MG) caused by COVID-19 vaccine had been reported, but the clinical course of new-onset ocular MG had never been described. We would like to document the clinical course of a patient with new-onset ocular MG which was caused by Pfizer–BioNTech COVID-19 vaccine.

Case report: A 39-year-old woman noticed diplopia one week after she accepted the first dose of Pfizer–BioNTech COVID-19 vaccine. Diagnosis of ocular MG was made after investigation. Despite intravenous immunoglobulins, pyridostigmine and prednisolone therapy, she had no improvement until 10 days after treatment. She then rapidly improved, and almost fully recovered in the following 10 days. We had observed this patient for 8 months. After tapering off steroid, she remained stable to date, though she still suffered from transient diplopia on awakening.

Conclusion: No matter the symptoms at onset, the clinical course or the response to steroid therapy was identical to ocular MG that we had ever known. Ocular MG caused by COVID-19 vaccine could probably be an iatrogenic life-long disease.

Keywords: **Myasthenia gravis, COVID-19 vaccination**

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INTRODUCTION

Myasthenia gravis (MG) is caused by antibodies attacking post-synaptic membrane proteins at neuromuscular junction, such as nicotinic acetylcholine receptors (AChR), muscle-specific tyrosine kinase (MuSK), agrin, and lipoprotein receptor–related protein 4 (LRP4). It is characterized by fatigability and weakness of the skeletal muscles, which can be focal or generalized and almost always includes extraocular muscles. The incidence of of MG is 8 to 10 cases per million persons. Systemic autoimmune disorders seem to occur with increased frequency in patients with MG of whom thyroid disorders are present in up to 15 percent[(1)].

When the clinical symptoms are isolated to the levator palpebrae superioris, extraocular, and orbicularis oculi muscles, it is referred to as ocular MG. More than half of all patients with MG initially present with isolated ptosis, diplopia, or both, whereas 15% to 49% of patients have isolated ocular MG as their only manifestation[(2)].

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Extensive research has shown the complex autoimmune nature of MG, but the precise mechanisms to trigger this disease are still unknown. Thymus is known to play a role, and T lymphocytes are responsible for initiating and maintaining the autoantibody response. New insights of pathobiology consist of genetic predisposition, upregulation of specific profiles of microRNAs and numerous cytokines, and the cellular responses after complement activation[1]. It has been well known the causes to worse pre-existing MG could be physiological (such as pregnancy), pathological (such as infection), or iatrogenic (such as medication, surgery and even vaccination).

COVID-19 was declared as a pandemic by World Health Organization (WHO) on 11 March 2020. Vaccination programs commenced globally in late 2020. As of 20 June 2022, more than 11 billion vaccine doses have been administered[3]. Sporadic cases of MG triggered or worsened by COVID-19 vaccination have been reported[4-11]. As of 25 June 2022, only 7 case reports of new-onset MG after COVID-19 vaccines have been reported[4, 5, 7, 8, 11, 12], and 3 of them were ocular MG[4, 7, 8]. It is worthwhile to pay more attention to these new-onset ocular MG because we do not know whether they would evolve into generalized MG or not. For this sake, we would like to report the clinical course of a case of new-onset ocular MG caused by the Pfizer–BioNTech COVID-19 vaccine. Afterwards we shall briefly review the published case reports of new-onset MG caused by COVID-19 vaccines.

CASE PRESENTATION

This 39-year-old women had suffered hypothyroidism and dry eyes for 10 years, and she was treated with Eltroxin 100 mcg every day to keep her in euthyroid state. Blood examination showed she had anti-thyroglobulin and anti-SSA antibodies. She appeared all normal despite the above problems, so she accepted the first dose of Pfizer–BioNTech COVID-19 vaccine on 16 October 2021. Visual problem developed one week after administration of vaccine. At the beginning, she had transient blurred vision which occurred when she was looking toward the left side. Diplopia soon became obvious. Five days after onset of symptom, she went to see an ophthalmologist who found her left eye could not look upwards. The other ophthalmological examinations were all normal. Next day she had right ptosis, so she came to see a neurologist. At that time, right ptosis was incomplete. On sustained upward test, there was movement like "reverse ocular bobbing" of the left eye (a phenomenon of mild weakness). She could have transient normal vision no more than several minutes after a night's rest, and otherwise diplopia and ptosis persisted all day without any change. Four days later, right ptosis became complete, and was associated with mild weakness of right lateral rectus muscle. Two more days later, this muscle also became completely paralytic. Ice packs held against both closed eyes for 5 min (ice pack test) could not improve ocular symptoms. Despite those ophthalmological problems, she had no subjective difficulty in speaking, swallowing, or breathing, and no other facial or proximal muscle weakness.

The diagnosis was ocular MG. A single-fiber electromyography (SFEMG) test from the right orbicularis oculi muscle identified an abnormal jitter in 5 of 18 muscle fiber pairs sampled. Anti-AChR antibody titer was negative (<0.2 nmole/L); anti-MuSK titer and anti-LRP4 titer were not examined. The result of repetitive stimulation test was normal. The computed tomography scan revealed no mediastinal mass.

During the acute stage, neither pyridostigmine (60mg three doses a day) nor intravenous immunoglobulins (0.4g/kg/day for 5 days) could improve her symptoms. She was then treated with prednisolone 40 mg every day. At first, right medial rectus muscle paradoxically became weak. She had no improvement until 10 days after treatment. Then ocular symptoms were getting better. Three weeks after steroid therapy, she almost fully recovered except that she had transient diplopia (lasting about 5-10 minutes) when she woke up after a night's rest or after a nap. Nonetheless, she kept on tapering the dose of prednisolone, and still could maintain in stable neurological condition. About 6.5 months later, she had COVID-19 viral infection. In addition to symptoms of upper airway, there was mild exacerbations of diplopia (subject worsening, without obvious change in extraocular movements), but no influence on swallowing, or breathing, and muscle powers of all limbs. One week later, diplopia recovered to baseline condition before COVID-19 infection. She maintained

in stable neurological condition to date, even though she was not completely free from diplopia. Pyridostigmine could not relieve such transient paradoxical diplopia after awakening.

DISCUSSION

In this patient, causal relationship between the onset of MG and the Pfizer–BioNTech COVID-19 vaccine was established on the basis of the following criteria: (1) a temporal association between administration of the Pfizer–BioNTech COVID-19 vaccine and the onset of symptoms of ocular MG existed; (2) symptoms developed within one week of vaccine administration (causality is defined by the WHO as less than 28 days)(13); and (3) no other potential triggers, including infection or new medications, were identified. To the best of our knowledge, this case ought to be the first one of new-onset ocular MG caused by Pfizer–BioNTech COVID-19 vaccine in the world.

Published literature verified both Oxford–AstraZeneca COVID-19 vaccines and Pfizer–BioNTech COVID-19 vaccines could precipitate new-onset MG or exacerbate pre-existing MG. In this report, we paid our attention to new-onset ocular MG. As of 25 June 2022, seven reports of new-onset MG caused by COVID-19 vaccines were found. Pfizer–BioNTech COVID-19 vaccines were related to 4 cases of new-onset generalized MG[5, 11, 12]. Galassi et al reported a coincidental ocular MG triggered by Oxford–AstraZeneca COVID-19 vaccine in a patient with pre-existing subclinical MG[8]. There were only 2 cases of new-onset ocular MG which were actually caused by COVID-19 vaccines, and both were precipitated by Oxford–AstraZeneca COVID-19 vaccines[4, 7]. Huang et al[7] reported a 53-year-old man with new-onset MG 1 day after the first dose of Oxford–AstraZeneca COVID-19 vaccination. Mahr and his colleague[4] reported a 52-year-old man with new-onset MG 1 day after the second dose of Oxford–AstraZeneca COVID-19 vaccine. All those 3 reports of new-onset ocular MG clearly described their symptoms at the onset, but none mentioned their clinical course after the diagnoses were made.

This patient's symptom began 1 week after administration of Pfizer–BioNTech COVID-19 vaccine. After onset, disability rapidly got worse and soon reached the nadir within 10 days. Thereafter, patient had had no improvement (at the nadir) for 16 days despite treatment with IVIg, pyridostigmine and prednisolone. Ten days after treatment with prednisolone 40 mg every day, patient began having improvement, and got almost full recovery in the following 10 days (treated with prednisolone 30 mg per day at that time). Although she had no recurrence of ptosis or worsening of diplopia during the period of tapering drugs, she had paradoxical diplopia on awakening. This patient had maintained at this plateau state for 8 months, except mild worsening of diplopia when she was suffering COVID19 viral infection.

We were still observing this patient when we were writing this case report. We were interested in clinical course because we once hypothesized if it was possible that the clinical course of vaccine-induced ocular MG was acute and monophasic, just as that of acute inflammatory demyelinating polyneuropathy. However, as 8 months had gone, she still had transient diplopia on awakening. Our hypothesis of acute monophasic course of illness became less likely; this vaccine-induced ocular MG could probably be a life-long iatrogenic disease. As we reviewed current literature, no article mentioned the clinical course of vaccine-induced ocular MG. We dared not to draw too assumptive conclusion from this case report, and we had to admit that this patient's manifestation was identical to ocular MG that we had ever known.

Although the pathology at the neuromuscular junction of ocular MG is not known to be distinct from generalized MG, there are several important and unique differences between them with regard to diagnosis and treatment. It is also uncertain why the disease stays localized to the extraocular muscles in patients with ocular MG. Distinguishing solely ocular myasthenia from generalized myasthenia soon after onset is challenging[1]. Of patients presenting with ocular MG, two-thirds will go on to develop signs and symptoms of extremity weakness and other bulbar muscle weakness, while one-third will continue to have pure ocular MG. Most (78 percent) of those who will develop generalized MG will do so within the first year, and 94 percent will do so within three years[1, 14, 15]. A normal SFEMG study may be helpful in stratifying risk of generalization. In one study of 37 patients with ocular MG followed for two years, 82 percent of those with normal SFEMG in the extensor digitorum communis persisted with isolated ocular MG, whereas 58 percent

of those with an abnormal study developed generalized MG[16].

To be or not to be vaccinated was a question for patients with autoimmune disorders[12, 17]. Vaccination poses a question whether vaccines containing pathogenic antigens can increase the risk of flare or exacerbate autoimmunity in susceptible individuals. As with this patient, a new autoimmune disorder could be triggered by a COVID-19 vaccine if patient had already suffered rheumatological problems. However, as we learned from these case reports, the incidence of vaccine-induced ocular MG was very low. Current cohort studies still emphasized the protection benefit of vaccination in patient with autoimmune diseases[18-20].

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