

Autoimmune myasthenia gravis after COVID-19 in a triple vaccinated patient

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ABSTRACT

Despite a well characterized mechanism, myasthenia gravis (MG) remains a dilemma in terms of etiology. Several case reports and series of cases suggest a potential cause-effect relation between SARS-CoV-2 infection or vaccination and MG. We present the case of an autoimmune MG occurring post Covid-19 in an elderly male, vaccinated with three doses of the BNT162b2/Pfizer-BioNTech vaccine. The 78-year-old male was admitted in the Neurology Clinic in early November 2021 with double vision, bilateral ptosis, dysphonia and dysphagia, 16 days after receiving a third dose of the BNT162b2/Pfizer-BioNTech SARS-CoV-2 vaccine and 12 days after testing positive for SARS-CoV-2 infection. The symptoms began to emerge at 9 days after COVID-19 diagnosis. Clinical neurological examination included ice-pack test and intramuscular neostigmine, both with positive results. Myasthenia gravis positive diagnosis was confirmed by slow repetitive nerve stimulation and abnormally increased serum levels of antibodies against acetylcholine receptors. Due to patient's refusal of further hospitalization, he was discharged with therapy recommendations. Under treatment with oral pyridostigmine, but no oral corticosteroid due to therapeutic noncompliance, the patient was readmitted two months later with aggravated symptoms. The myasthenic crisis was successfully treated with intravenous immunoglobulins, corticosteroid therapy and oral pyridostigmine. The novelty of the current case resides in the fact that, to the best of our knowledge, appears to be the first case of MG clinically manifested after COVID-19 infection in a fully vaccinated patient.

KEYWORDS: post-infectious autoimmune myasthenia gravis; COVID-19; SARS-CoV-2 vaccination; cause-effect relationship

INTRODUCTION

March 2020 marks the moment when Coronavirus disease 2019 (COVID-19) was officially declared a pandemic by the World Health Organization [1]. From a neurological point of view, SARS-CoV-2 might represent the missing link in decoding the causes of several still idiopathic diseases, as an increasing number of observational studies report cases of Miller-Fischer Syndrome, Guillain-Barré Syndrome, myopathies and myasthenia gravis (MG) following COVID-19 [2-4].

Even though acquired autoimmune MG is an archetypal autoimmune neurological disease, its causes still remain an undefined territory. According to present knowledge, MG is considered a consequence of interactions between genetic and exogenous factors mediated by epigenetic mechanisms [5]. A number of viruses are proposed as plausible etiological candidates that interact initially with the toll-like receptors of the innate immune system of the host [6]. At least

theoretically, autoimmunity in MG, as in other autoimmune diseases, is triggered by molecular mimicry, epitope spreading and innocent bystander activation [7]. Of all the viruses proposed, Epstein Barr virus remains the most plausible candidate due to its ability to stimulate activation and survival of B lymphocytes [8].

Taking into consideration that there seems to be a strong, yet unclearly defined connection between MG and COVID-19, we present in this case report what is, to the best of our knowledge, the first case of autoimmune MG following altogether COVID-19 and third dose BNT162b2/Pfizer-BioNTech SARS-CoV-2 vaccination.

CASE REPORT

A 78-year-old male with a negative history of autoimmune disorders, both personal and of collateral inheritance, presented in the Emergency Room at the Emergency clinical Hospital Prof. Dr. N. Oblu, Iasi on the first of November 2021 with double vision, bilateral ptosis, dysphonia and dysphagia. On October 15th 2021 he received the third dose

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BNT162b2/Pfizer-BioNTech SARS-CoV-2 vaccination at approximately seven months after the second dose. On October 19th 2021 he was tested positive for SARS-CoV-2 infection (reverse transcriptase polymerase chain reaction, RT-PCR, from nasopharyngeal swab) in a clinical context of fever, myalgia and dry cough within the last 24 hours. He was diagnosed with a mild form of COVID-19 and discharged with supportive therapy (oral vitamins, oral antiplatelet agent) that led to a favorable evolution, with complete symptoms remission in 5 days. However, nine days after COVID-19 diagnosis he developed acute-onset diplopia, asymmetrical bilateral ptosis, dysphonia and dysphagia, with no reported diurnal variation and a progressive evolution during the following four days (Figure 1).

General examination was within normal parameters. The neurological examination revealed general muscular fatigability, with positive effort tests and clear modifications of the cranial nerves: asymmetrical bilateral ptosis (second degree right and first degree left), horizontal bilateral double vision, but with normal ocular motility, discrete nasal intonation, mild dysphagia for both solids and liquids, with reduced pharyngeal and palatal reflexes. The rest of the neurological examination did not show any other pathological modifications. Ice-pack and intramuscular neostigmine test were performed, both with positive results.

Peripheral blood cell count did not suggest any form of immunodeficiency. Magnetic resonance imaging (MRI) of the brain did not reveal any lesions that could explain the clinical panel. Slow repetitive nerve stimulation (RNS) of *right nasalis* muscle revealed an abnormal decrementing response between 17.3%-20.8% (Figure 2). Serum levels of antibodies against acetylcholine receptors (RAch) were elevated (19.2 nmol/L as opposed to normal <0.25nmol/L) whereas serum levels of other MG-associated antibodies remained within normal laboratory parameters (anti-titin, other striated muscle fiber and anti-muscle specific tyrosine-kinase receptor, MuSK). The thyroid function was normal. Contrast thoracic computed tomography (CT) did not find

any thymic abnormalities. Corroborating the history, clinical features and paraclinical data, the patient was diagnosed with MG, class IIB according to the modified Osserman clinical classification of the Myasthenia Gravis Foundation of America, with a Myasthenia Gravis Activities of Daily Living profile (MG-ADL) score of 7 [9]. Due to the fact that both the patient and his family refused further hospitalization, he was discharged with recommendations of oral pyridostigmine 240 milligrams daily and oral prednisone 20 milligrams daily.

As the patient refused prednisone intake at home, two months later, on the January 10th 2022, the patient returned to the emergency room due to a prior two weeks acute onset and a progressive course of an aggravated diplopia, bilateral ptosis, dysphagia for both liquids and solids and dyspnea (Figure 1). RT-PCR SARS CoV-2 was repeated from a nasopharyngeal swab and tested negative. Chest CT revealed neither pulmonary abnormalities, nor thymic modifications. However, due to rapid aggravation of symptoms, especially dyspnea with an arterial oxygen saturation of 85%), the patient was admitted in the intensive care unit, he was intubated and mechanically ventilated and intravenous immunoglobulins were administered (0.4 g/kg/day for five days), together with oral methylprednisolone 64 milligrams/day and oral pyridostigmine 240 milligrams/day, with a gradual regression of myasthenic symptoms. Beginning with day 7 of hospitalization the patient was extubated. He was discharged after 15 days with an MG-ADL score of 2 and with indication of oral methylprednisolone 48 milligrams/day and oral pyridostigmine 240 milligrams/day.

DISCUSSION

We hereby present the case of an elderly male with ocular and bulbar manifestation of MG after a mild form of COVID-19. The particularity of the case resides in the fact that prior to myasthenic manifestations the patient received

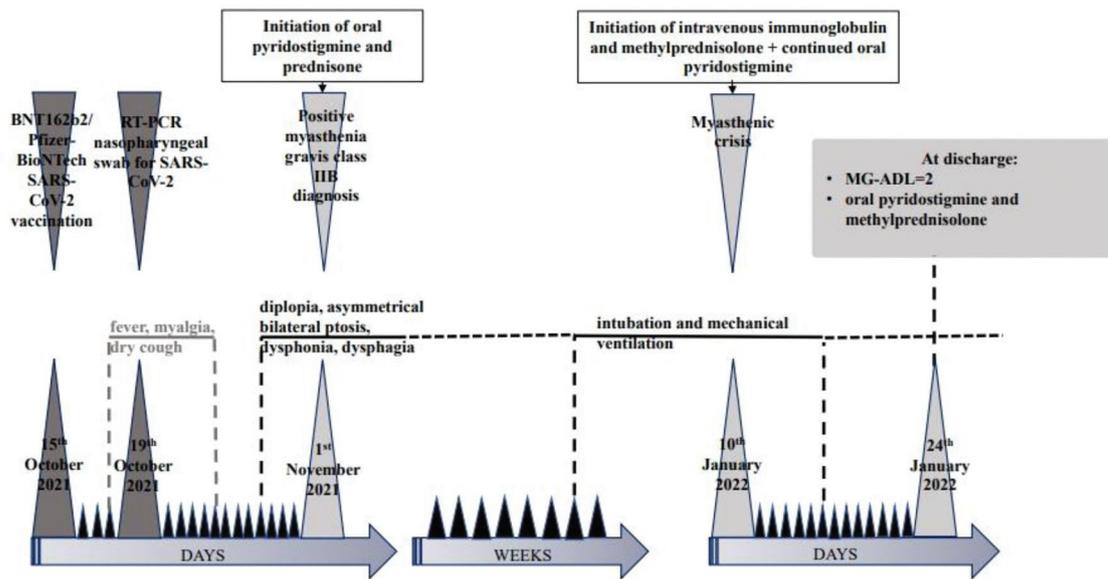
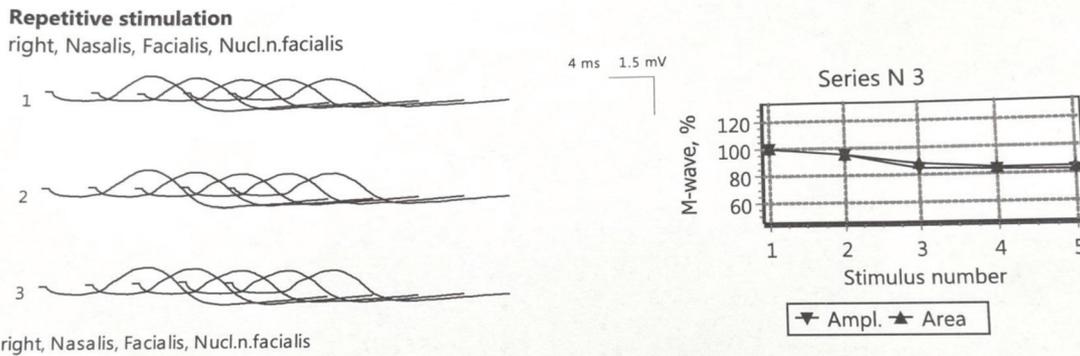


Fig. 1. Timeline of major events in the recent history of the case: SARS-CoV-2 vaccination, COVID-19 positive diagnosis, onset of class IIB myasthenia gravis followed by successfully treated myasthenic crisis.

Summary EMG data

Repetitive stimulation											
Test	Series N	Stim. time, s	Freq., Hz	Stim. number	Decrement	Baseline ampl., mV	Ampl decr., % (1-5)	Ampl decr., % (1-last)	Baseline area, mV×ms	Area decr., % (1-5)	Area decr., % (1-last)
right, Nasalis, Facialis, Nucl.n.facialis											
2	1	00:00	3.0	5		1.27	20.8	20.8	4.7	18.6	18.6
	2	00:10	3.0	5		1.33	20.1	20.1	5.3	23.2	23.2
	3	00:20	3.0	5		1.31	17.3	17.3	4.8	15.1	15.1
right, Abductor digiti minimi, Ulnaris, C8 T1											
1	1	00:00	3.0	5		11.7	1.9	1.9	56.3	2.6	2.6
	2	00:14	3.0	5		11.8	3.7	3.7	57.0	6.6	6.6

Decrement-test



right, Nasalis, Facialis, Nucl.n.facialis

Repetitive stimulation (amplitude: peak-to-peak)

Series N	Stim. time, s	Freq., Hz	Stim. number	Decrement	Baseline ampl., mV	Ampl decr., % (1-5)	Ampl decr., % (1-last)	Baseline area, mV×ms	Area decr., % (1-5)	Area decr., % (1-last)	Stim., mA	Stim., ms
1	00:00	3.0	5		1.27	20.8	20.8	4.7	18.6	18.6	20	0.2
2	00:10	3.0	5		1.33	20.1	20.1	5.3	23.2	23.2	25	0.2
3	00:20	3.0	5		1.31	17.3	17.3	4.8	15.1	15.1	25	0.2

Repetitive stimulation
right, Abductor digiti minimi, Ulnaris, C8 T1

Fig. 2. Abnormal decrementing response at slow repetitive nerve stimulation of right Nasalis muscle.

the third BNT162b2/Pfizer-BioNTech SARS-CoV-2 dose vaccination. At this time, there is no certainty regarding which of the two is a more plausible culprit, nor even if any of them could be a culprit at all. Long-term follow-up of post-infectious and post-vaccine new-onset MG cases could clarify the dilemma. It could be argued that myasthenic syndrome is a one-time post-infectious and/or post-vaccine acute episode rather than a new onset chronic autoimmune disease. However, development of a myasthenic crisis in the absence of corticosteroids administration tends to favor the latter explanation.

Arguments for MG triggered by SARS-CoV-2 infection or vaccination against it reside in the case reports scattered in the medical literature published since the beginning of SARS-CoV-2 pandemic. Regarding vaccination, several cases of apparently new-onset MG have been reported in both Caucasians and non-Caucasians [10-12]. A recent search through PubMed/Medline database for cases and series of cases of new-onset MG following SARS-CoV-2 infection revealed a total of fourteen patients originating from Europe, North America and Asia. Overall, the time interval between COVID-19 and development of myasthenic signs and symptoms ranges from 3 to 56 days [4,13-21].

Though highly probable, the cause-effect relationship between SARS-CoV-2 infection and MG is currently under debate. Several mechanisms have been postulated for explaining how SARS-CoV-2 could trigger and/or amplify autoimmunity in MG. However, according to current medical literature, a combination of cross-reactivity between SARS-CoV-2 antigens and human self-peptides and breakdown in self-tolerance due to T regulatory lymphocytes dysfunctions appear to be the most plausible causes [22]. In the current case presented, the time interval between both SARS-CoV-2 vaccination and infection and onset of MG supports this theory.

CONCLUSION

In the current study we present what it appears to be, to the best of our knowledge, the first case of MG clinically manifested after COVID-19 infection and third dose SARS-CoV-2 vaccination. Even though at the moment no direct causality relationship can be established between these 2 disorders, the increasing number of new-onset MG cases following COVID-19 or vaccination against it raises a hypothetical connection that deserves further attention.

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Conflict of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Ethics Statement

According to the local legislation and institutional requirements, the patient provided his written informed consent for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

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