New-onset Myasthenia Gravis after SARS-CoV-2 infection: case report and literature review

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Abstract
We report the case of a 19-year-old female patient who developed Myasthenia Gravis 13 days after SARS-CoV-2 infection with positive RT-PCR testing. Her symptoms initially involved the oculo-bulbar district, but they gradually worsened in 3 months converting into a generalized form of Myasthenia Gravis complicated with a myasthenic crisis. A high level of anti-acetylcholine receptor antibodies was found in the serum, while anti-MuSK antibodies were negative; Repetitive Nerve Stimulation and Single-fiber Electromyography were suggestive of Myasthenia Gravis. Intravenous immunoglobulin courses and specific therapy were able to improve her symptoms, but thymic resection was needed to control the disease. This is a report of new-onset Myasthenia Gravis correlated to COVID-19 in which thymic resection was described and the histologic analysis of the thymus was performed showing thyinic hyperplasia despite negative thoracic Magnetic Resonance Imaging. SARS-CoV-2 infection releases inflammatory cytokines that could dysregulate the immune system and lead to Myasthenia Gravis in susceptible subjects.

Keywords Myasthenia Gravis · COVID 19 · SARS-CoV-2 · Myasthenic Crisis · Postinfectious Myasthenia Gravis · Neuromuscular disorders

Abbreviations
MG Myasthenia Gravis
SARS-CoV-2 Severe acute respiratory syndrome coronavirus 2
MGFA Myasthenia Gravis Foundation of America
RT-PCR Reverse transcriptase-polymerase chain reaction
MRI Magnetic Resonance Imaging
CT Computed Tomography
MGC score Myasthenia Gravis composite score
IVIg Intravenous immunoglobulin
ENT Ear, nose and throat
MRC Muscle Power assessment
MCD Mean consecutive difference
ATD Autoimmune thyroid disease
VATS Video-assisted thoracoscopic
AChR Acetylcholine receptor
LRP4 Low-density lipoprotein receptor-related protein 4
MuSK Muscle-specific tyrosine kinase
IL-7 Interleukin-7
IL-21 Interleukin-21
IL-6 Interleukin-6
IL-23 Interleukin-23
TGD-b Tumor Growth Factor beta
CSI Chemical-shift imaging

Introduction
Myasthenia Gravis (MG) is a post-synaptic neuromuscular junction disease caused by the production of antibodies against the components of the post-synaptic membrane. The most common form includes antibodies against post-synaptic extracellular portions of the nicotinic acetylcholine receptor (AChR).

In the literature, the debut of MG in connection with a specific infection has been reported in several case series.
Some of the patients reported having thymoma as a cofactor and others were familiar with autoimmune diseases. In general, microbes are thought to precipitate an unwanted immunological response against self-antigens. Molecular mimicry, epitope diffusion, and polyclonal activation have all been suggested as responsible for the induction of MG by viral agents, but the exact mechanisms have not been proven. Moreover, no correlation between a specific preceding infection and MG has been documented [1]. The SARS-CoV-2 virus infection [2] has been correlated to several neurological manifestations, including neuropsychy, myopathy, Guillain-Barré syndrome, anosmia, ageusia, and neuromuscular disorders [3]. Few cases of New-onset Myasthenia Gravis after COVID-19 have been reported [4–13]. The authors speculated that the new-onset MG after COVID-19 could be explained by molecular mimicry [4–6, 8–11, 13, 14] or by the breakdown of self-tolerance mechanisms [4, 9, 10, 12–14] as a consequence of the infection. Others supported the possibility that COVID-19 could have triggered latent MG [4, 9, 10, 12, 13]. Here, we present a case of new-onset oculo-bulbar MG after SARS-CoV-2 infection which rapidly converted to generalized MG class IIIb, according to MGFA classification [15]. To our knowledge, this is the first reported case of generalized MG and thymic hyperplasia developing after COVID-19 infection. We have also tried to give our interpretation regarding the possible immunological interactions between infection, myasthenic onset, and pathology of the thymus. Namely, we hypothesized an imbalance between T lymphocytes after COVID-19 infection, which could have stimulated AChR overexpression, promoting anti-AChR antibody production.

Case report

A 19-year-old woman presented to our Neurological Outpatient Clinic in June 2021 with complaints of fluctuating diplopia, moderate dysarthria, moderate dysphagia for solids, right ptosis, and generalized weakness which have begun in March 2021. Her medical history included Hashimoto’s Thyroiditis, thalassemia, iron-deficiency anemia, and autoimmune gastritis. Her medication history comprehended iron supplements with ferrous sulfate, levethyrooxine, and folic acid; her Body Mass Index (BMI) was 21. She was not vaccinated against SARS-CoV-2.

Before coming to our outpatient clinic in late June, she contracted SARS-CoV-2 (COVID-19) infection on March 7th, 2021, (which presented) with mild respiratory symptoms of dyspnea, sore throat, hyposmia, dysgeusia, fever, and cough. After 10 days, her respiratory symptoms regressed and SARS-CoV-2 molecular testing on the nasopharyngeal swab (reverse transcriptase-polymerase chain reaction or RT-PCR) resulted negative. Thirteen days after the RT-PCR positivity to SARS-CoV-2 infection, she developed fluctuating fatigable symptoms consisting of diplopia, moderate dysarthria, moderate dysphagia for solids, and right ptosis but no limb weakness. The severity of the symptoms fluctuated during the course of the day and improved after rest. Swallowing and chewing were difficult, and the patient lost 10 kg of weight. At that time, she performed brain Magnetic Resonance Imaging (MRI) scans that showed an 8 mm pineal cyst and pituitary hyperthrophy; ENT and oculist examinations were unremarkable and endocrinological examination excluded hyperplutilus. In June, the symptoms worsened involving the limbs too.

On neurological examination (performed on June 21st), the patient presented bilateral ptosis with incomplete eyelid closure and prominent peek sign at rest; she had nasal speech, but there was not dysarthria or dyspnea. She was not able to crouch down or walk on her toes or heels. Sensation, stretch reflexes, muscle tone, and tropism were normal. When muscle strength was assessed, we detected moderate weakness (Medical Research Council grade 3) with shoulder abduction, elbow flexion, wrist extension, hip flexion, knee extension, and foot dorsiflexion bilaterally. Fatigability was tested: single-breath count aloud determined dysarthria and hypophonia after 18 s, sustained up-gaze and lateral-gaze resulted in horizontal diplopia after 5 s, shoulder abduction was maintained for 13 s, and hip flexion for 4 s. Elevation of the neck from the bed while lying supine was completely impaired. Her Myasthenia Gravis Composite score (MGC score) was 26/50 [16]. MG was suspected based on the clinical presentation. Facial and ulnar Repetitive Nerve Stimulation (RNS) showed a 60% and 37% decrement, respectively, and single-fiber electromyography (SFEMG) of the frontalis muscle demonstrated a markedly prolonged jitter (Mean Consecutive Difference or MCD = 103 μs) compatible with the diagnosis of Myasthenia Gravis (see Fig. 1).

The patient was hospitalized to start intravenous immunoglobulin (IVIg); however, on her second day of hospitalization, she developed a Myasthenic Crisis with hypercapnic respiratory failure and she was transferred to the intensive care unit where she was intubated, treated with IVIg (0.4 g/Kg/die for 5 days) and corticosteroids (Prednisone 1 mg/Kg/die). Before the Myasthenic Crisis, the patient was not assuming specific therapy for MG. After 7 days of admission, her vital signs improved, and she was extubated; the patient was then transferred to our semi-intensive care unit where she started pyridostigmine 60 mg QID and reduced prednisone to 60 QD. Ten days after her admission, the patient was discharged from our semi-intensive care unit with oral pyridostigmine 60 mg QID, oral pyridostigmine extended release 180 mg and Prednisone 50 mg, which she continued after discharge from the hospital, with her symptoms improved and steady vital signs. Thoracic MRI performed during the hospitalization excluded thymoma or...
thymic hyperplasia. Circulating anti-AChR antibodies in her serum were > 5 mMol/L (normal value < 0.25 mMol/L), while anti-Muscle-Specific Tyrosine Kinase (anti-MuSK) antibodies were negative. The patient was readmitted to our unit in late August and early December with the complaint of worsening diplopia, bilateral ptosis, and severe weakness of her upper and lower limbs without bulbar symptoms; on these occasions, she was treated with a course of IVIg (0.4 g/Kg/die). During her last hospitalization, the case was discussed with the thoracic surgeons and the patient underwent thymectomy, according to the guidelines [17], with the Video-Assisted Thoracoscopic Surgery (VATS) approach in mid-December 2021, when her symptoms were under sufficient control and she was able to undergo surgical procedure.

She was discharged with oral pyridostigmine 60 mg QID and prednisone 50 mg QD; thymic histology of a surgical specimen showed diffuse lympho-follicular hyperplasia (see Fig. 2).

During the follow-up, her symptoms gradually improved. In her last neurological examination performed in April 2022, she was able to crouch down 5 times consecutively without effort, MRC was 5/5 in all the examined districts,

Fig. 1 A Baseline 3 Hz repetitive nerve Stimulation (RNS) test of the right Abductor digiti Minimi Muscle of the hand (Ulnar Nerve) shows a decremental response of 37% consistent with neuromuscular junction transmission defect. B Single-fiber EMG (SFEMG) of a pair of adjacent single muscle fibers registered from the right Frontalis Muscle (20 superimposed rastered traces) shows increased Jitter (102 μs); after the registration of more couples, we obtained an overall MCD of 103 μs.
eyelid closure was normal, she was able to lift off her head from the bed for 60’ and single count aloud without hypophonia or dysarthria for 60 s, sustained up-gaze determined bilateral ptosis and horizontal diplopia after 32 and 45 s, respectively, sustained lateral-gaze-evoked horizontal diplopia after 38 s in both sides, sustained abduction of the arms and elevation of the legs was performed for 33 and 40 s, respectively. Her MGC score was 6/50; prednisone was then gradually reduced to 30 mg QD, while the pyridostigmine dosage remained unchanged. The timeline is shown in Fig. 3.

**Discussion**

There are 11 reports (see Table 1) describing a total of 15 patients (9 males and 6 females) with new-onset MG, potentially induced by SARS-CoV-2 infection [4–14]. The mean age of the patients was 55.9 years (range 21–71), while the mean latency from COVID 19 infection to the development of Myasthenic symptoms was 23 days (range 5–60). COVID-19 symptoms were mild in ten patients and severe in two patients; in three patients, the severity of SARS-CoV-2 infection symptoms was not assessed. Only, in two cases, there was evidence of thymoma on thoracic Computer Tomography (CT) and the patient was referred to surgery, but the outcome is unknown in one of them. A thymic histology was performed in only one of them and only after the thymoma was confirmed on thoracic CT. 13 patients were positive for anti-AChR antibodies (1 of them was positive for both anti-AChR antibodies and anti-titin antibodies) and 2 patients were positive for anti-MuSK antibodies. RNS testing was the only neurophysiological investigation to be performed in nine patients, and in eight of them, the results were consistent with the diagnosis of MG [5, 6, 9, 10], while in only one case, it was normal [8]. In three cases, both SFEMG and RNS were performed with a compatible result [4, 12, 13]. In one case, only SFEMG was performed [7], while in two cases, both RNS and SFEMG were not performed [11, 14]. The MG manifested as generalized muscle weakness in 11 patients; three patients presented

Fig. 2 Shows the thymic histology with diffuse lympho-follicular hyperplasia. A H&E landscape 100×magnification shows thymic architecture with the presence of germinative centers with polarization in lymphoid follicles; B the immunostain (immunoperoxidase with pankeratin antibody cocktail CAM5.2) shows bulging epithelial thymic clusters at the periphery of lymphoid follicles; C immunostain for CD20 highlights the mature B lymphocytes component; D immunostain for CD23 shows a dendritic follicular cells population resembling lymphoid hyperplasia in lymph node. H&E Hematoxilin and Eosin, CAM pankeratin cocktail immunoperoxidase
with the pure ocular pattern and only one presented with the oculo-bulbar form. One patient presented history of Pernicious Anemia and Addison’s disease and one more patient had familiarity for other autoimmune disease. Five patients initially needed at least one course of IVIg [5, 8, 10, 12, 14] and two patients underwent Plasmapheresis [5, 6]. Twelve patients were treated with pyridostigmine and/or prednisone as an initial therapy or after IVIg/plasmapheresis [4–10, 12–14] and three patients needed azathioprine in addition [9, 10, 13]. For one case, the therapy was not described [11]. All the patients were reported to be improved after therapy.

Some of the authors speculated that the new-onset MG after COVID-19 could be explained by molecular mimicry [4–6, 8–11, 13, 14] or by the breakdown of self-tolerance mechanisms [4, 9, 10, 12–14] as a consequence of the infection. Actually, in some cases, infections can precede or exacerbate MG [1], but the hypothesized mechanisms in MG have not been proven. Some of the authors supported the possibility that COVID-19 could have triggered latent MG [4, 9, 10, 12, 13].

In our case, the onset of the MG was 13 days after SARS-CoV-2 positivity to nasopharyngeal swab RT-PCR. However, it is possible to assume that she contracted the infection a few days before this confirmation. She developed anti-AChR antibodies and the thoracic MRI did not show thymic pathological findings on Chemical Shift Imaging (CSI). Comparing to CT in which 45% of thymic hyperplasia cases are not detected [18], chemical-shift displacement-MRI has recently revealed promising capabilities to distinguish thymic hyperplasia from thymomas. However, in some cases of young women, this technique is not able to distinguish normal thymus from thymic hyperplasia [19]. CSI is able to detect microscopic fat infiltration, which develops with age and could be insufficient in young patients to observe a decrease in signal. Therefore, this technique is not fully reliable in young subjects and could lead to false negatives [20]: for this reason, the histological examination is the needed to perform the diagnosis. In all the other previous reports [4–14], the patients underwent thoracic CT and not MRI to detect thymic pathology. Therefore, similarly to our case before surgery, the involvement of the thymus could not be excluded only on the ground of imaging results. It is important to highlight this is the first case of new-onset MG, potentially induced by SARS-CoV-2 infection, associated with thymic hyperplasia. The medical history of our patient included Hashimoto’s Thyroiditis, thalassemia, iron-deficiency anemia, and autoimmune gastritis. Many studies reported the increased prevalence of autoimmune disorders in MG and autoimmune thyroid disease (ATD) seems to be the most associated pathology. The etiology of both diseases is multifactorial, and it is due to genetic and environmental factors. Moreover, in both MG and ATDs, T-cell immune-mediated mechanisms are involved. Patients with early onset MG seem to have higher frequency of a second autoimmune disorder than patients with late onset MG and thymic hyperplasia is a marker for an increased risk. This suggests that the patient had a predisposition to the development of autoimmune diseases, which favored the disruption of self-tolerance after COVID-19 infection [21–23].

There is evidence that the thymus is involved in the pathogenesis of MG in the subset of patients with anti-AChR antibodies and viral infections could trigger the onset of MG; thymic epithelial cells can express cross-reactive epitopes with skeletal muscle proteins, and these are presented to T lymphocytes; in a second step, thymic cells activate antigen presenting cells and diversify the antibody response. Viral infection could affect the initial expression of muscle-like epitopes within the thymus, as well as T lymphocytes’ regulation and thus initiate the immunization process [1, 24]. Similarly, in our patient, SARS-COV2 infection could have triggered thymic inflammation, influencing the initial expression of muscle-like epitopes, as well as T-cell dysregulation. In particular, in patients with COVID-19, there is a tendency for enhanced thymic function in producing T lymphocytes in comparison to controls, as a result of adaptation to virus-related...
Table 1  Shows the list of the studies in which new-onset MG was preceded by SARS-CoV-2 infection

| Author                  | Gender/age | Medical history                                                                 | Latency from COVID-19 infection to MG symptoms (days) | COVID-19 infection severity and symptoms | MG presentation | MG-related Abs          | Thymus pathology on Chest-CTa or Biopsyb | RNS and/or SFEMG diagnostics |
|-------------------------|------------|----------------------------------------------------------------------------------|-------------------------------------------------------|------------------------------------------|----------------|--------------------------|------------------------------------------|----------------------------|
| Restivo et al. [5]      | M/68y      | N/A                                                                              | 7                                                     | Mild; fever for 7 days                   | Generalized MG | Anti-AChR Abs+           | Noa                                      | Facial RNS 57% decrement; SFEMG not performed |
|                         | M/64y      | N/A                                                                              | 5                                                     | Mild; fever for 4 days                   | Generalized MG | Anti-AChR Abs+           | Noa                                      | Facial RNS 52% decrement; SFEMG not performed |
|                         | M/71y      | N/A                                                                              | 5                                                     | Severe; cough and fever for 6 days       | Generalized MG | Anti-AChR Abs+           | Noa                                      | Facial RNS 21% decrement; SFEMG not performed |
| Huber et al. [8]        | F/21y      | Familiarity for Hashimoto's thyroiditis, pernicious anemia, Addison's disease    | 10                                                    | Mild; anosmia, ageusia, diarrhea, aching of limbs and head for less than a month | Ocular MG     | Anti-AChR Abs+           | Noa                                      | Facial RNS normal; SFEMG not performed |
| Perez Alvarez et al. [11]| M/48y      | Positive ANA; Schizophrenia and inverse Psoriasis                              | 15                                                    | Mild; fever, cough and dyspnea for 5 days | Ocular MG     | Anti-AChR Abs+           | Noa                                      | RNS or SFEMG not performed               |
| Assini et al. [13]      | M/77y      | N/A                                                                              | 56                                                    | Severity N/A; fever and dyspnea for less than 42 days | Oculobulbar MG| Anti-AChR Abs -          | Anti-LRP4 Abs +                          | RNS and SFEMG consistent with MG          |
| Muhammed et al. [12]    | F/24y      | N/A                                                                              | 28                                                    | Mild; influenza like symptoms (duration N/A) | Generalized MG| Anti-MuSK Abs +         | Anti-LRP4 Abs -                          | Ulnar RNS and facial SFEMG consistent with MG |
| Muralidhar et al. [10]  | M/65y      | Diabetes and Hypertension                                                       | 42                                                    | Mild; cough, fever and cold for about 2 weeks | Generalized MG| Anti-AChR Abs +         | Anti-MuSK Abs -                          | Facial RNS 41% decrement; accessory nerve RNS 18.1% decrement |
| Sriwastava et al. [4]   | F/65y      | Meningioma; Pituitary adenoma; pulmonary carcinoma; left RCC                    | 11                                                    | Severe; Diarrhea and Myalgia for 2 weeks  | Ocular MG     | Anti-AChR Abs +         | Anti-MuSK Abs -                          | Facial RNS and SFEMG consistent with MG   |
| Author                                | Gender/age | Medical history                                   | Latency from COVID-19 infection to MG symptoms (days) | COVID-19 infection severity and symptoms | MG presentation | MG-related Abs | Thymus pathology on Chest-CT\(^a\) or Biopsy\(^b\) | RNS and/or SFEMG diagnostics |
|---------------------------------------|------------|--------------------------------------------------|------------------------------------------------------|-----------------------------------------|-----------------|---------------|--------------------------------------------------|-----------------------------|
| Karimi et al. [6]                     | F/61 y     | N/A                                              | 32                                                   | Severity NA; respiratory symptoms for 5 days | Generalized MG  | Anti-AChR Abs+ | Thymoma\(^a\)                                    | Facial, median and accessory nerve RNS 15–27% decrement, SFEMG not performed |
|                                       | M/57 y     | CHF and ICD                                       | 6                                                    | Mild; fatigue, fever and dry cough for 6 days | Generalized MG  | Anti-AChR Abs+ | No\(^a\)                                         | Facial, ulnar, median and radial RNS 10–40% decrement, SFEMG not performed |
|                                       | F/38 y     | N/A                                              | 28                                                   | Mild; myalgia, fatigue, cough and fever (duration N/A) | Generalized MG  | Anti-AChR Abs+ | Anti-MuSK Abs −                                   | Facial and radial RNS 30–40% decrement SFEMG not performed |
| Bhandarwara et al. [14]               | M/61 y     | Diabetes Mellitus and Bronchial asthma           | 60                                                   | N/A                                                   | Generalized MG  | Anti-AChR Abs+ | Thymoma\(^a\)                                    | N/A                          |
| JÖGI et al. [9]                       | M/65 y     | Hypertension, hypercholesterolemia, cataract     | 14                                                   | Mild; fever, cough and dyspnea (duration N/A)       | Generalized MG  | Anti-AChR Abs+ | Anti-titin Abs +                                  | Facial RNS > 50% decrement, ulnar RNS 5–10% decrement, accessory nerve RNS 26–29% decrement; SFEMG not performed |
| Taheri et al. [7]                     | F/35       | N/A                                              | 27                                                   | Mild; fever, myalgia, sore throat, dyspnea, cough for 13 days | Generalized MG  | Anti-AChR Abs+ | No\(^a\)                                         | SFEMG consistent with MG; RNS not performed |
| Current report                        | F/19 y     | Hashimoto’s thyroditis, thalassemia, autoimmune gastritis, anemia | 13                                                   | Mild; dyspnea, sore throat, hyposmia, dysgeusia, fever, and cough for 10 days | Oculobulbar and then Generalized MG | Anti-AChR Abs+ | Anti-MuSK Abs −; negative thoracic MRI | Facial RNS 60% decrement, ulnar RNS 37% decrement; SFEMG frontalis muscle MCD = 103 μs |

\(^a\)Thymus pathology investigated with thoracic CT

\(^b\)Thymus pathology investigated with biopsy

MG Myasthenia Gravis, AChR acetylcholine receptor, LRP4 low-density lipoprotein receptor-related protein 4, MuSK Muscle-specific tyrosine kinase, RCC renal cell carcinoma, ANA antinuclear antibodies, RNS repetitive nerve stimulation, SFEMG single-fiber electromyography, N/A data not available
lymphopenia [25]. This event is possibly correlated to the increase of IL-7 concentration in the plasma of COVID-19 patients [25]; IL-7 is a factor important for the survival and proliferation of immature thymocytes but also for T-cell receptor rearrangement during early development [26, 27]. Moreover, COVID-19 could induce an increased expression of cytokines and a chemokines’ storm (Tumor Growth Factor beta, Interleukin 6, Interleukin 23) and angiogenesis among stromal and T cells of the thymus, contributing to the attraction of B cells from the periphery [28]. The inflammatory environment modulates an imbalance among T cells in favor of T-helper 17 cells; the high production by Th17 cells of interleukin-21 (IL-21) could stimulate the development of T follicular helper cells, and the overexpression of acetylcholine receptor (AChR) promotes the anti-AChR antibody production [29]. This succession events could lead to thymic hyperplasia and MG, probably as a consequence of the production of pro-inflammatory factors that could have dysregulated the immune system and altered the self-tolerance.

In our patient, we hypothesize that the SARS-COV2 infection could have triggered thymic inflammation, influencing the initial expression of muscle-like epitopes as well as T-cell dysregulation. Moreover, a latency shorter than a week from the onset of infection to the onset of myasthenic symptoms typically could represent the effect of the pre-existent memory B cells that produce low-affinity antibodies involving the non-specific immune response; on the contrary, a latency longer than a week could be the expression of the adaptive immunity [30]. The latency of the new-onset MG and the gradual evolvement of myasthenic symptoms in our patient could be compatible with a mechanism involving adaptive immunity.

However, it is not possible to exclude that the viral infection precipitated a pre-existing immune response, unmasking a latent Myasthenia Gravis. The causal relationship between the two conditions is difficult to establish. In any case, the coexistence of other autoimmune pathologies represents a predisposing factor for both pathological mechanisms described.

In conclusion, our case, in line with those reported in the literature, suggests that COVID-19 infection can accelerate the new onset of MG. Evidence from more case series would be important to analyze the pathological timeline and the immunological characteristics of COVID-19-induced MG.

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Declarations

Conflicts of interest The authors declare that they have no conflict of interest.

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