COVID

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Case Report

New Onset Generalized Myasthenia Gravis Evolving Following SARS-CoV-2 Infection

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Abstract: During the SARS-CoV-2 (COVID-19) pandemic, the immunogenicity of the virus for various autoimmune complications has been observed. To date, a few reports have been published that raise the possibility of new onset myasthenia gravis (MG) associated with COVID-19 infection. We report a case of a 65-year-old male who developed his initial myasthenic presentation with mild dysarthria 14 days after COVID-19 infection symptomatic onset. His bulbar symptoms, diplopia, and ptosis progressed considerably over the next 1.5 months before he was diagnosed with non-thymomatous MG. Serological tests showed a high concentration of anti-acetylcholine receptor and anti-titin antibodies. He responded well to treatment with pyridostigmine and intravenous immunoglobulin. Reasonable latency from COVID-19 infection and gradual evolvement of myasthenic symptoms makes the causative association probable in this case. To our knowledge, this is the first report of anti-titin antibodies in new-onset MG associated with COVID-19 infection. In the article, we analyze the previously reported cases and summarize the information published to date. We discuss the possible immunological mechanisms behind new onset autoimmune disease following a viral infection and the associated features that raise the suspicion for such a possibility. We also hint at structural homologies between SARS-CoV-2 spike glycoprotein and titin epitopes.

Keywords: myasthenia gravis; SARS-CoV-2; acetylcholine receptor; titin; antibodies; autoimmunity

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1. Case Report

In this report, we would like to present a case of a 65-year-old Caucasian male who fell ill with fever, cough, and shortness of breath. His general practitioner referred him to SARS-CoV-2 (COVID-19) RNA-testing, which was positive. Genotyping of the detected virus strain was not possible in retrospect, however, based on epidemiological data the causative strain was likely *delta*. The patient had previously opted not to vaccinate himself against COVID-19. On the ninth day of symptoms, his condition deteriorated with exacerbation of dyspnea. The patient was admitted to the nearest county hospital with symptomatic COVID-19 infection. His past medical history was unremarkable with hypertension, hypercholesterolemia, and cataract. Regular medication included daily perindopril/amlodipine/indapamide 5 mg/10 mg/1.25 mg, metoprolol 50 mg and atorvastatin 20 mg.

In the local county hospital, the patient was diagnosed with pneumonia from COVID-19 infection and symptomatic treatment was started, including dexamethasone 6 mg daily for five days. The condition of the patient improved with treatment, he needed additional oxygen 2–4 L/min and did not need mechanical ventilation. During fifth day in hospital, the patient noticed problems with speech. He described difficulty pronouncing words and dysarthric slurring lasting only for a couple of minutes at a time. The symptoms were inconsistent with only a couple of similar recurrencies. Because of these new symptoms and suspicion of transitory ischemic attacks, he was transferred to the neurology department of the same hospital.

In the neurology ward, the slurring did not reoccur and there were no significant neurological complaints or findings. The patient was studied for risk factors for an ischemic attack—brain CT, brain MRI, cardiac monitoring for arrhythmias, transesophageal echocardiography were performed. The studies did not reveal any additional risk factors, except higher blood glucose. As the speech difficulties did not reoccur, the patient was discharged on the 18th day in the hospital. He was additionally diagnosed with a transitory ischemic attack and was started on treatment with aspirin.

While at home, the patient developed further symptoms within a month. He first noticed diplopia; thereafter, he developed consistent speech slurring. The symptoms worsened on repetition or prolonged activity, e.g., when speaking. Nevertheless, he did not report clear diurnal variation with worsening towards the end of the day. Consequently, he developed difficulty swallowing, being only able to eat soft foods. Eventually, he developed weakness of neck muscles, having difficulties holding up his head. The patient was admitted once again to the neurology department of his nearest county hospital 1.5 months after his first hospitalization.

In the county hospital records, the findings described bilateral ptosis, right-sided oculomotor paralysis, dysarthria, dysphagia, weakness of neck muscles. Nerve conduction studies (NCS) and electromyography (EMG) by an experienced neurophysiologist were not possible at the time. Additional blood tests and cerebrospinal fluid analysis were performed—the only significant finding was a high concentration of acetylcholine receptor (AChR) antibodies, >20 nmol/L (reference value <0.44 nmol/L). On chest CT, no signs of a thymoma or thymus hyperplasia were seen, his thymus was completely involuted.

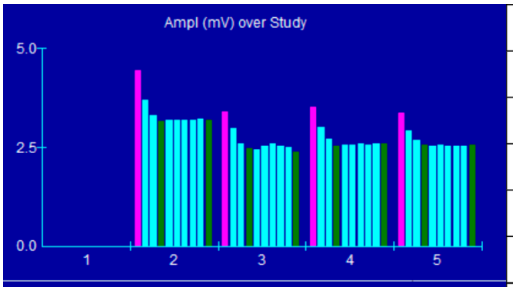
He was started on prednisolone and also received a 5-day course of intravenous immunoglobulin (IVIg) with a total dose of 180 g. In the following days, his symptoms vastly improved—the only residual symptom being ptosis on the left. On the 12th day in the hospital, the patient was discharged. There was no description of any remaining symptoms on that day. Although EMG was not a diagnostic requisite, he was not prescribed pyridostigmine at that time and was scheduled for an outpatient EMG and a neurologist's appointment.

Thereafter, his symptoms with diplopia and bilateral ptosis gradually worsened again. Three months later the patient had an out-patient visit to a pulmonologist for a post-COVID-19 infection check-up where no signs of secondary pulmonary complications were evident. However, the pulmonologist referred him to a neurologist at the Tartu University Hospital after which he was directly admitted to the Tartu University Hospital neurology department with myasthenia gravis (MG) exacerbation.

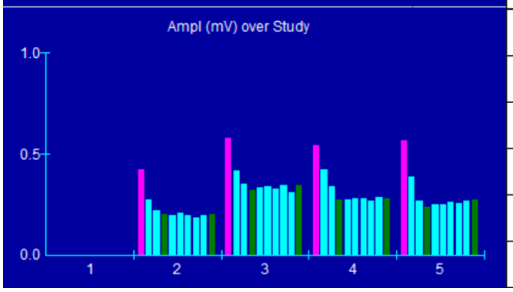
On admission, the patient presented with severe dysarthria (speech was partly incomprehensible), bilateral ptosis, more evident on the left, and diplopia on lateral gaze in both directions. The patient did not complain of shortness of breath or dyspnea. He had, however, lost about 10 kg of weight in the preceding three months. There was clear bilateral weakness of orbicularis oculi and dysphagia. His Myasthenia Gravis Composite (MGC) score was 16 points. EMG showed a significant decrement on repetitive nerve stimulation—abductor digiti minimi 5–10%, trapezius 26–29%, orbicularis oculi over 50% (Figure 1). There was no incremental response, nor suggestion for myopathy. The findings were conclusive for generalized MG. On the same day, the patient had a radiological swallowing assessment, showing moderate dysphagia with solid consistency in the pharyngeal phase and nasal regurgitation with liquids. On the same day, after the EMG, the patient was started on pyridostigmine 60 mg three times a day. The next day the patient showed clear signs of improvement—dysarthria had almost resolved; swallowing had significantly improved, and diplopia was less severe.

During the next few days, his symptoms were gradually improving. He was started on azathioprine 50 mg daily. In addition to the strong positivity of AChR antibodies of over 20 nmol/L (negative reference range <0.44 nmol/L) on repeated testing, the patient had also strong positivity of titin antibodies (on semi-quantitative analysis 138 arbitrary units, negative reference range <16 arbitrary units). He also met diagnostic criteria for

type II diabetes. Troponin T was only slightly elevated 21.7 ng/L (negative reference range <14 ng/L). Other laboratory tests, such as thyroid function tests, vitamin B12, other autoimmune tests, including anti-nuclear antibodies, were within normal range. For academic purposes, HLA haplotype analysis identified susceptible allele groups, linked with late-onset MG, as follows: DQA1*01,*04 and DQB1*04,*05. His SARS-CoV-2 IgG concentration at the time was 3711 kU/L (negative reference range <50 kU/L).



R Accessory (spinal) - Trapezius 3Hz 10x				
Train	Rate	Ampl mV	Ampl 1–4%	Area mVms
Baseline	3	4.4	−28.7	42.3
Post-exercise	3	3.4	−26.8	31.6
1 min	3	3.5	−27.9	32.8
2 min	3	3.4	−23.2	30.4



R Facial - Orbicularis oculi 3Hz 10x				
Train	Rate	Ampl mV	Ampl 1–4%	Area mVms
Baseline	3	0.4	−52.5	1
Post-exercise	3	0.6	−44.8	0.8
1 min	3	0.5	−49.7	0.8
2 min	3	0.6	−57.8	1.1

Figure 1. Significant decremental response to repetitive nerve stimulation (3 Hz) of the right trapezius and orbicularis oculi on electromyography.

The patient was discharged on the fifth day of the in-patient stay. The only remaining symptom was mild ptosis on the left (Figure 2). The patient had no major swallowing difficulties and his speech was nearly normal with minimal fatigue during the longer conversation. The final treatment plan included up to 6 tablets of 60 mg pyridostigmine a day and 100 mg azathioprine a day. He was scheduled for a follow-up neurology appointment in four weeks.

Figure 2. Patient with AChR and titin antibodies-associated myasthenia gravis: residual ptosis on the left after initiating treatment with pyridostigmine. Informed written consent for publication was obtained from the patient.

2. Overview of Myasthenia Gravis and SARS-CoV-2 Infection

MG consists of a group of autoimmune disorders that all include disturbances of the postsynaptic neuromuscular junction involving auto-antibodies. The prevalence of these diseases is 15 to 179 cases per million [1]. The most common form includes antibodies against postsynaptic nicotinic AChR [2]. Additional autoantibodies have been uncovered,

the most common being muscle-specific tyrosine kinase (MuSK) and low-density lipoprotein receptor-related protein 4 (LRP4) antibodies which damage different structures of the neuromuscular junction, but the presenting clinical findings are similar [2]. Seronegative cases of MG still carry a high suspicion of involvement of unknown antibodies [2].

AChR antibodies are polyclonal IgG, directed against extracellular portions of the AChR, usually the α-subunit [3,4]. They are produced by plasma cells, derived from B cells, in peripheral lymphoid organs and bone marrow. Existing memory B cells are activated by re-presentation with antigen (or similar epitopes, such as viral), and reciprocally, by similarly activated autoreactive T cells. No consistent correlation has been shown between the titer of AChR antibodies and the disease severity [5]. The pathogenicity of antibodies in MG depends on the antibody specificities and is conveyed partly via activation of the complement-mediated cascade.

Anti-titin IgG, considered as secondary autoantibodies in MG, can be found in approximately 50% of late onset AChR-MG without a thymoma [6–8]. Titin antibodies react with intracellular protein antigens within striated muscle and bind mostly to a region located near the A-I junction [9]. Their pathogenetic role remains unclear, however, they have been shown to correlate more with disease severity than AChR antibodies and may identify cases more likely to be refractory to the therapy [10]. Titin antibodies have not been reported with anti-MuSK-MG and are rarely found in young onset MG [10].

The clinical course of MG depends on the involved antibodies that react with multiple determinants [11]. The different antibody-mediated forms of MG have differences in age of onset, MG clinical pattern, associated thymus pathology, and other co-morbidities [11]. MG usually first manifests in smaller muscles—orbicularis oculi, facial muscles, pharyngeal muscles [12]. The presenting symptoms in generalized MG can include diplopia, ptosis, change in voice, and difficulties in swallowing and can progress to involve bigger striated muscles in limbs and body, including respiratory muscles [11].

During the COVID-19 pandemic, there has been a rising concern for exacerbations of previously diagnosed MG due to superimposed severe viral infection [13]. However, only a few reports have been published to date on de novo MG that is induced by SARS-CoV-2 [14–20]. In the reported cases of new onset MG following COVID-19 infection, variable clinical presentations and several autoantibodies have been shown.

Using the OVID Medline Database (https://ovidsp.ovid.com, accessed on 9 November 2021), we found 9 case reports that describe a possible connection between SARS-CoV-2 infection and new onset myasthenia gravis [14–20]. The summary of these cases is presented below (Table 1). The age and gender distribution of these patients is diverse: 6 men and 2 women have been reported, the oldest being 77-year-old and the youngest 21-year-old [14–20]. Most of these patients had a mild COVID-19 infection, except for two patients who had a severe infection, while only one patient needed mechanical ventilation [14–20]. The latency between the first SARS-CoV-2 and MG symptoms were between 5 to 56 days, the median being 11 days [14–20]. The patients had a variety of MG symptoms, primarily generalized (5 cases) [14–20], 4 patients had only ocular or oculobulbar symptoms [14–20]. Serological findings showed AChR antibodies in 7 cases, MuSK antibodies in two cases [14–20]. Only in one case report anti-titin antibodies were assessed and were negative [15]. Thymus pathology was not found in any of these cases [14–20]. Several possible pathogenesis theories were discussed, the main hypotheses being overactive inflammatory response leading to pathological antibody production and possible molecular mimicry mechanism between the epitopes of SARS-CoV-2 virus and the structures of the neuromuscular junction [14–20].

Table 1. Summary of previously published cases of myasthenia gravis presenting after SARS-CoV-2 infection.

Author	Age/Gender	COVID-19 Infection Severity	Latency of MG Symptom Onset	MG Presentation	MG Serological Findings	Thymus Pathology
Restivo et al., 2020 [18]	64/M	mild	5 days	generalized	AChR Abs +	none
	68/M	mild	7 days	generalized	AChR Abs +	none
	71/M	severe	5 days	generalized	AChR Abs +	none
Sriwastawa et al., 2021 [19]	65/F	severe	11 days	ocular	AChR Abs +	none
Huber et al., 2020 [15]	21/F	mild	10 days	ocular	AChR Abs +, titin Abs -	none
Muralidhar Reddy et al., 2021 [17]	65/M	mild	42 days	generalized	AChR Abs +	none
Perez Alvarez et al., 2020 [20]	48/M	mild	15 days	ocular	AChR Abs +	none
Assini et al., 2021 [14]	77/M	NA	56 days	oculobulbar	MuSK Abs +	none
Muhammed et al., 2021 [16]	24/F	mild	28 days	generalized	MuSK Abs +	none

Adapted from Muralidhar Reddy et al., 2021 [17]. MG—Myasthenia Gravis; AChR—Acetylcholine receptor; MuSK—muscle-specific tyrosine kinase; Abs—antibodies; NA—not available

3. Discussion

Several similarities exist between the previously reported cases and our case of a 65-year-old male who developed his first likely myasthenic symptoms 14 days after symptomatic onset of his relatively mild COVID-19 infection. In previously published cases, the latency from infection to MG symptoms has been reported between 5 to 56 days [14–20]. Longer latency could be considered more supportive of new onset MG, as opposed to pre-existing latent disease, since infection-precipitated full-blown generalized MG may take several weeks to develop.

Time interval less than a week from infection onset to MG manifestation largely represents the effect of innate immunity with less antigen-specific humoral responses [21]. This innate response, also called extra-follicular (EF) B cell response, is mediated by low-affinity antibodies, and depends on the presence of the pre-infection memory B cell repertoire [22]. An alternative explanation to a shorter latency could be an existing MG that is unmasked by an infection.

Memory T and B cells to particular self-antigens reside in the bone marrow and peripheral lymphoid tissues. In a developing disease state, they are activated by the representation of specific antigen epitopes together with co-stimulatory signals at germinal centers of secondary lymphoid organs. As the population of new generation B cells and long-lived plasma cells develop over an average of two weeks, the immune response becomes more antigen-specific, resulting in a more targeted antibody response, also called germinal center (GC) B cell response [21,23,24]. This late antibody response becomes more dominant with a latency of weeks and months. However, in the setting of severe COVID-19 infection, EF responses could be relatively more persistent than GC responses [22,25].

In that regard, the sequence of developing symptoms in our case from first episodes of speech slurring as the first presentation of MG to a full-blown disease may illustrate the above processes on an immunopathological timeline. As an alternative, an underlying existing MG cannot be ruled out either in this case as a possibility.

Prolonged pro-inflammatory response to an infection is considered a predisposing factor to autoimmune complications together with genetic susceptibility, often linked to a particular HLA haplotype, involved in antigen presentation [26]. Late onset MG has been previously linked with HLA DQA1 in several populations [27–29]. HLA DQB1 allele variants have been associated with predisposition to different subtypes of MG [30,31].

In our patient, the analysis of HLA DQA1 and DQB1 loci revealed predisposing allele groups (HLA DQA1*01,*04 and DQB1*04,*05), explaining the susceptibility in this case for developing MG.

One of the mechanisms underlying presumed immune pathology in COVID-19 precipitated MG is molecular mimicry, i.e., the similarity of self-antigens to that of a precipitant viral epitope, involving both humoral and cellular immunity. Priming of the immune system and the inflammatory milieu are important for susceptibility of molecular mimicry mechanism resulting in autoimmune disease. Several other mechanisms may be involved in infection-induced autoimmunity.

Little is known to date about titin IgG as secondary antibodies in MG and their pathogenicity. Development of anti-titin IgG after COVID-19 infection may be the result of molecular mimicry, or a phenomenon called epitope spreading as the disease evolves. The exact causative mechanism remains unclear. Interestingly, structural homology between SARS-CoV-2 and titin has been shown and hypothesized in the COVID-19 induced autoimmunity [32]. The article by Kanduc describes 29 pentapeptides that are shared both by titin and SARS-CoV-2 spike glycoprotein [32]. This could suggest that autoimmune response to titin, in fact, may also have been triggered by COVID-19. Slight raise in troponin T was detected in our patient but the cardiac status was otherwise normal, including echocardiography findings. Troponin raise may occur in conjunction with other secondary antibodies to muscle protein.

To our knowledge, this is the first case of anti-titin IgG have been described with MG following COVID-19 infection. Striational antigen epitopes, such as that of titin, may be involved in COVID-19 induced autoantigen sensitization. The potential role of anti-titin autoimmune response yet remains to be elucidated in active COVID-19 infection, or as a post-COVID-19 manifestation, considering this structural homology.

The presence of anti-titin IgG together with AChR IgG generally suggests higher likelihood of thymus pathology in myasthenic patients. As in other published cases, our patient did not have a pathological thymus on chest CT-scan. In fact, the thymus in our case was involuted and indetectable, replaced by fatty tissue in the thymic compartment. Hence, regarding an association of titin IgG positivity and thymus pathology, our case is in line with thymus unassociated pathology.

Considering the possibility that some medication can exacerbate existing MG, our patient received azithromycin in the county hospital. According to the hospital records, he received it after the first symptoms that possibly were his first presentation of MG. Additionally, the fact that he received azithromycin only for 4 days makes it an unlikely causative factor. Azithromycin and other macrolides can worsen myasthenic symptoms by blocking acetylcholine release in the neuromuscular junction [11]. In these cases, the exacerbation of MG is almost immediate, and the effect would disappear after stopping the administration of the drug [33]. The patient did not receive any other medications that could have worsened his myasthenic symptoms.

The causal relationship between the two conditions is difficult to establish, however, the fact that MG did not present in the acute phase of COVID-19 infection but rather started to develop in the resolving phase of infection could support new onset MG in this case. We see the clear gradual evolvement of symptoms in our case to active generalized MG with reasonably explained latency and consistency with possible underlying immunological mechanisms. Additionally, an autoimmune response to titin, and its potential association with SARS-CoV-2 spike glycoprotein structural homology, is intriguing.

In conclusion, COVID-19 infection may precipitate new onset MG. The immunogenicity of COVID-19 for autoimmune complications requires further studies. Evidence from additional reports would be valuable to analyze the pathological timeline and associations of COVID-19 induced secondary autoimmunity. Specifying the involved EF and GC responses would also allow to better define the latency for possible emerging autoimmune conditions. Regarding MG, epidemiological evidence from cohorts of COVID-19 patients is needed to indicate whether the incidence of MG is higher in that population.

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