Case Report

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Remission of myasthenia gravis following infection with SARS-CoV-2

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Abstract:

This case report describes an unprecedented remission of ocular Myasthenia Gravis (MG) in a 3-year-old girl following a SARS-CoV-2 infection. Both MG and SARS-CoV-2 influence the cholinergic system, and this case underscores the importance of considering multiple factors in autoimmune disorders and the potential impact of viral infections on their course. The patient initially presented with ptosis and limited eye movement. Her diagnosis of seronegative MG was confirmed with abnormal visual evoked potentials and positive response to pyridostigmine. Her ptosis and limited extraocular muscle movement were intermittent until 2 years later when she tested positive for SARS-CoV-2 for which no antiviral medication was taken. Unexpectedly, her MG symptoms rapidly improved postinfection, leading to the cessation of pyridostigmine. This case highlights the complex interplay between MG, viral infections, and the influence of anti-acetylcholine receptor antibodies, second-hand smoke, and natural nicotinic agonists from the use of pyridostigmine on the cholinergic system.

Keywords:

Acetylcholine, myasthenia gravis, remission, SARS-CoV-2, spontaneous

Introduction

Myasthenia Gravis (MG) is the most common autoimmune neuromuscular disease leading to skeletal muscle weakness. The range of symptoms varies from a solely ocular manifestation to profound weakness in the limbs and respiratory muscles. To date, there have been numerous cases of recurrent or new-onset MG following infection with SARS-CoV-2. However, we are documenting the first reported case in which MG symptoms entered a state of remission following a COVID-19 infection, possibly resulting from the interplay between multiple elements associated with the cholinergic system.

Case Report

On August 17, 2020, a 3-year-old girl came to the pediatric outpatient department at Mackay Memorial Hospital, reporting 2 weeks of ptosis, particularly in her left eye, and occasional exotropia in the same eye. She had moderate ptosis in her left eye but no strabismus with a full range of extraocular movement. The pediatrician initially suspected MG based on her clinical presentation. Her symptoms greatly improved with 30 mg of pyridostigmine three times daily.

This patient had a complex diagnostic course. The anti-acetylcholine receptor (AchR) antibody assay yielded a negative result (<0.20 nmole/L); however, the evoked potentials examination revealed a significantly prolonged latency of the P100 visual evoked potentials (VEPs) waveform on her left side [Figure 1]. An ultrasound ruled out the presence of a thymoma. The extraocular muscles later became involved [Figure 2].

The patient was given a diagnosis of MG given her response to medical therapy and abnormal VEP exam. However, the parents were inconsistent with the prescribed

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Goggle-VEP 2Y-4Y

Protocol / Run	N1 ms	P1 ms	N2 ms	P2 ms	N1-P1 μV	P1-N2 μV
L - VEP-Goggles						
1.1 O1 - Fz						
1.2 Oz - Fz	73.13	139.69	191.25		17.1	23.5
Ref.		105.00		8.00		
1.3 O2 - Fz						
1.4 Cz - Fz						
R - VEP-Goggles						
1.1 O1 - Fz						
1.2 Oz - Fz	63.75	109.69	190.94		13.0	14.7
Ref.		105.00		8.00		
1.3 O2 - Fz						
1.4 Cz - Fz						

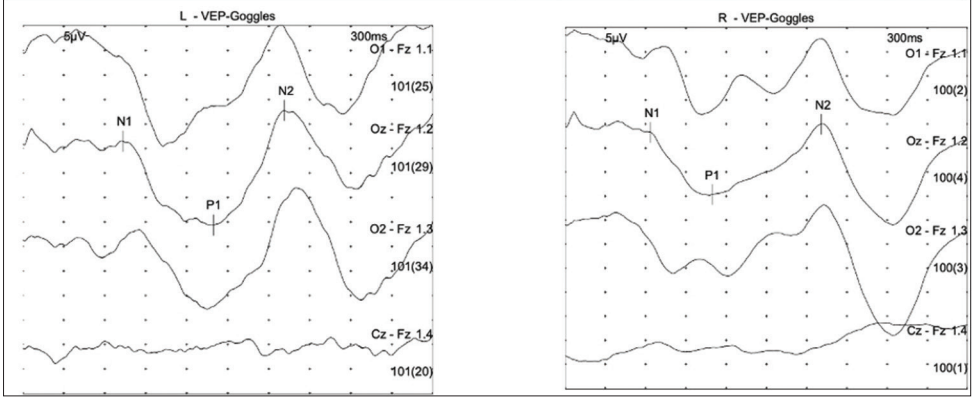

Figure 1: Asymmetrical prolongation of P100 visual evoked potential latencies, with a more significant delay on the left side compared to the right side

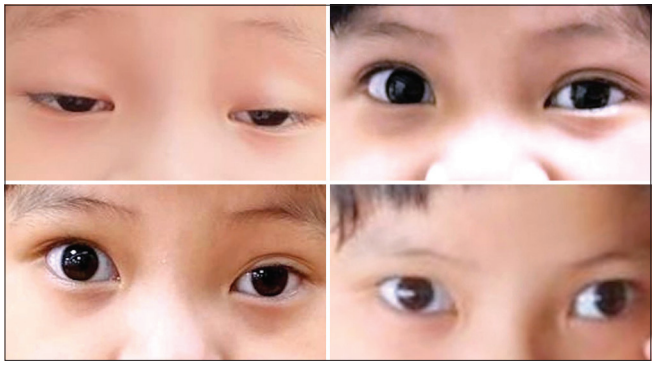

Figure 2: Images taken at home showing early stages of the patient's clinical course. Ptosis and abnormal extraocular range of motion affecting both eyes intermittently

medication and adjusted the dosage based on the patient's condition. She experienced intermittent disfiguring ptosis, severe exodeviation (possibly greater than 45 prism diopters according to the parents' description and home photographs), and limited extraocular movements that impacted her daily life until she tested positive for SARS-CoV-2 infection on June 15, 2022. According to her parents, her symptoms significantly improved after 1 month, and they chose to discontinue the administration of pyridostigmine. Her symptoms returned once the medication was discontinued but to a much milder degree.

The patient presented to the ophthalmology department of Mackay Memorial Hospital for a strabismus evaluation on March 24, 2023. The prism cover test revealed an exodeviation of 30 prism diopters and a hypotropia of 8 prism diopters in her left eye at the primary position. Limited extraocular movement in the left eye was observed during supraduction and adduction, implying that the left superior rectus, left medial rectus, and left inferior oblique muscles were involved. No ptosis was detected in either eye [Figure 3]. She was emmetropic, and she had 20/20 distance vision in both eyes.

In a phone interview on August 16, 2023, the parents reported that since contracting COVID-19, the ptosis has not returned, and the limitation in extraocular movement has gradually improved. She is now managing her daily life with only a mild strabismic condition and often experiences temporary full recovery without any medication. The parents noted that she has not taken pyridostigmine since her first full recovery in July 2022 and provided home photos from the period of full recovery [Figure 4]. At this point, it was revealed that the patient's father is an in-home tobacco user. Of note, the patient denied receiving any antivirals or the COVID-19 vaccine.

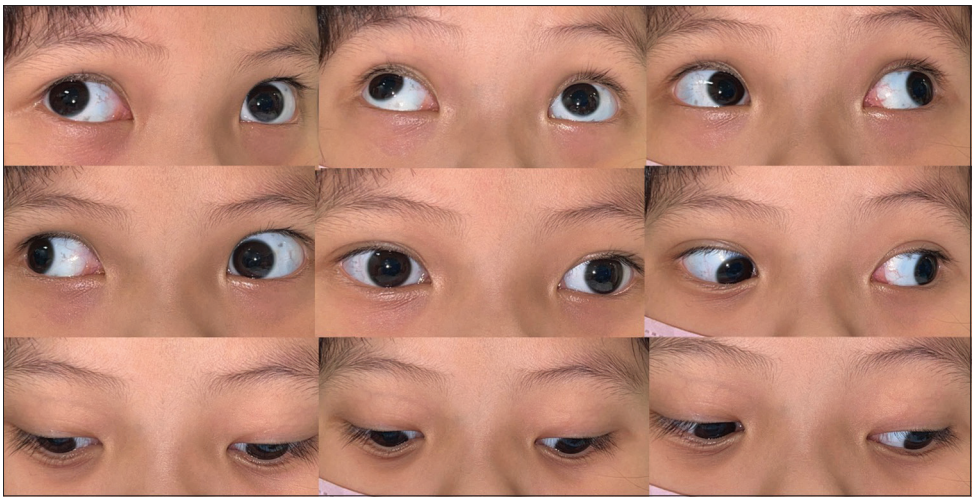

Figure 3: Images captured in the ophthalmology clinic when the patient was 6 years old, 9 months after she stopped taking pyridostigmine following a COVID-19 infection. Exotropia and left hypotropia with limited abduction and supraduction were still evident in the left eye

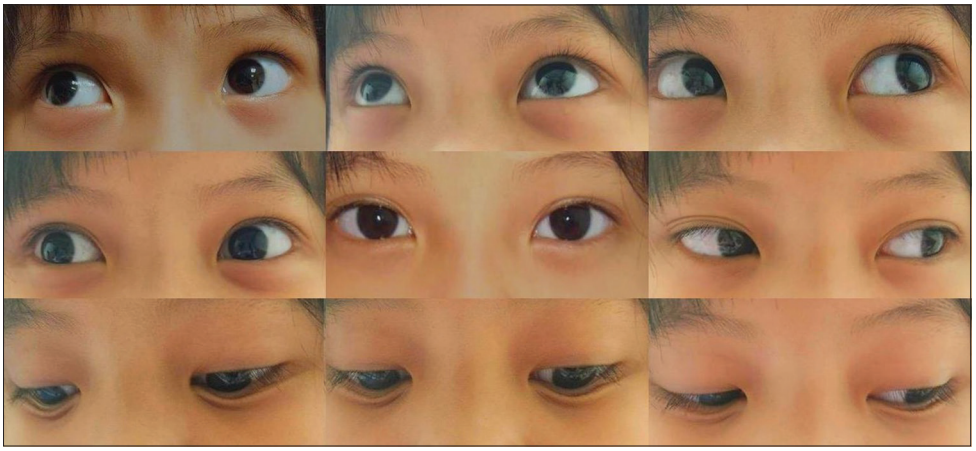

Figure 4: Images provided by the patient's parents claiming that she is now managing her daily life with only strabismic condition and often experiences temporary full recovery without any medication

Discussion

We report the first documented case of MG remission following a COVID-19 infection. Approximately 85% of patients with clinical manifestations of MG test positive for antibodies, commonly against the AChR, while around 15% remain seronegative.[1,2] Clinical profiles generally do not differ significantly between seropositive and seronegative patients, although those with isolated ocular symptoms often exhibit lower titers of anti-AChR antibodies. Seronegativity may also result from low-affinity antibodies targeting AChRs. For symptomatic but seronegative patients, abnormal VEPs have been used to suggest potential central nervous system (CNS) involvement.[3] Pattern reversal VEP has also been employed as a method to monitor CNS improvement in MG following pyridostigmine therapy.[4] When additional diagnostic confirmation is necessary, invasive electrophysiological techniques, such as repetitive nerve stimulation and electromyography, can be utilized.

In our case, the 3-year-old patient exhibited asymmetrical prolongation of P100 VEP latencies, with more pronounced delays on the affected side, indicating impaired CNS-level signal transmission likely associated with MG. Despite being seronegative, the patient with isolated ocular symptoms responded favorably to pyridostigmine, the gold standard treatment in MG management.

The pathophysiology of MG involves the immune system mistakenly producing antibodies against native nicotinic AchRs (nAChRs) at the neuromuscular junction, disrupting normal nerve-muscle communication. Acetylcholine, a neurotransmitter released by motor neurons at the neuromuscular junction, normally binds to nAChRs to initiate action potentials that enable muscle movement. In MG, autoantibodies against AChR compete with acetylcholine for binding to nAChRs. This competition can lead to the destruction or internalization of nAChRs, reducing the number of functional receptors

on the muscle cell membrane and further impairing muscle function.

Most of the literature focuses on patients with new-onset MG following SARS-CoV-2 infection, which is drastically different from our case.[5] The exacerbation or recurrence of MG symptoms may be linked to the presence of angiotensin-converting enzyme 2 receptors, the cellular entry point for SARS-CoV-2, on the surface of various cells, including those in the respiratory and cardiovascular systems.[6]

Notably, there exists a protective mechanism known as the "cholinergic anti-inflammatory pathway." This regulatory process involves communication between the nervous and immune systems, facilitated primarily by the vagus nerve and α7nAChRs. α7nAChR is an AchR subtype found on immune cells such as macrophages and T-lymphocytes that initiates anti-inflammatory signaling pathways, thereby attenuating the overall inflammatory response.[7]

In 2020, Farsalinos *et al*. conducted a study in which they modeled the pathogenesis of severe COVID-19. They identified a sequence alignment between the spike glycoprotein of SARS-CoV-2 and NL1, a neurotoxin homolog found in snake venom. Their investigation involved *in silico* molecular docking simulations to explore the potential binding between SARS-CoV-2 and nAChRs.[8] At the cellular level, evidence suggests a direct interaction between SARS-CoV-2 and nAChRs. This interaction implies that SARS-CoV-2 might exploit the cholinergic system, specifically nAChRs, to induce immune dysregulation, potentially triggering a cytokine storm – a hallmark of severe COVID-19.

However, evidence of this interaction suggests the virus, which would inhibit the immune pathway and could cause reduced antibody production. Although disruption of antibody production can impair the immune system, it may also inadvertently decrease the production of autoantibodies, which correlates with the alleviation of MG symptoms in this instance.

In this unique case, remission of MG symptoms followed a COVID-19 infection, suggesting a potential causal link rather than a mere coincidence. COVID-19 is typically associated with exacerbation or onset of MG symptoms; however, this case is distinctive, as the patient exhibited stable yet unimproved symptoms for nearly 2 years before infection. Remarkably, within 1 month of contracting COVID-19, the patient's clinical condition showed substantial improvement, implying a direct impact of the infection on disease progression. Although full remission required additional time, COVID-19 appears to have initiated a significant turning point in the clinical course. In typical MG management, substantial clinical improvement often necessitates prolonged treatment, with medication courses frequently exceeding 33 months using agents like prednisolone or immunosuppressants.[9] In contrast, this case demonstrated an unusually rapid response, suggesting that COVID-19 infection may have exerted an unexpected therapeutic effect. Given these distinctive features, it is reasonable to differentiate this remission from the spontaneous remission typically observed in ocular MG.

Another possible explanation for the patient's MG remission is her exposure to nicotinic agonists, such as second-hand cigarette smoke. It has been suggested that nicotinic agonists like cigarettes or caffeine may inadvertently contribute to relief in SARS-CoV-2 infection and MG.[8,10,11] Small amounts of nicotinic agonists could potentially act as triggers for the anti-inflammatory response.[7,8] Finally, prior administration of pyridostigmine, an acetylcholinesterase inhibitor, may have contributed to the preservation of potentially impaired nAChRs, thereby aiding in the eventual alleviation of MG symptoms.

One limitation of this case report is the negative AChR antibody result, with the diagnosis heavily relying on abnormal VEP findings. While amblyopia could theoretically contribute to abnormal VEPs, no signs of amblyopia were observed by the patient's parents, and she exhibited emmetropic vision with 20/20 visual acuity bilaterally. Thus, it is unlikely that a preexisting visual condition influenced the VEP results. The diagnosis was further supported by initial clinical signs, including bilateral ptosis and a rapid response to pyridostigmine. This diagnosis was subsequently substantiated by a relapse of ptosis and limited extraocular movement following the reduction of pyridostigmine before her SARS-CoV-2 infection.

Another limitation is the absence of genetic testing, which would aid in differentiating between congenital myasthenic syndrome (CMS) and juvenile MG. Given the patient's age of <3 years, distinguishing between these conditions is crucial. CMS is favored as the likely diagnosis due to the early onset of symptoms and the rarity of JMG in this age group. CMS typically results from genetic mutations affecting neuromuscular transmission, making genetic testing highly valuable for diagnostic confirmation.[12]

Furthermore, while only the standard AChR antibody assay was performed, broader antibody testing could provide additional diagnostic insights. Expanding the investigation to include assays for other neuromuscular junction-related antibodies, such as those targeting

muscle-specific tyrosine kinase, low-density lipoprotein receptor-related protein 4, or other relevant markers, would enhance diagnostic accuracy and yield more comprehensive information. This approach is particularly relevant given the rarity of ocular MG in young children without an identifiable genetic cause.

Our objective is to document a case of MG remission following SARS-CoV-2 infection. This case underscores the intricate interactions between clinically diagnosed MG, viral infections, and the cholinergic system. It highlights the potential influence of anti-AchR antibodies, environmental tobacco smoke, and prior pyridostigmine use. Additional research is required to substantiate whether the remission of MG following SARS-CoV-2 infection can be attributed to molecular mimicry. It is crucial to emphasize that this hypothesis remains speculative, as there is currently no definitive evidence supporting this mechanism. The relationship between SARS-CoV-2 and autoimmune disorders like MG is complex and not fully understood. Moreover, any potential alleviation of MG symptoms through this mechanism would need to be weighed against the risks and complications associated with SARS-CoV-2 infection and both first- and second-hand cigarette smoke.

Declaration of patient consent

This study was conducted in accordance with the ethical principles outlined in the Declaration of Helsinki and its amendments. The authors certify that they have obtained appropriate consent forms from the legal guardians of the patient(s). In the form, the guardians have given consent for the images and other clinical information of the patient(s) to be reported in the journal. The guardians understand that the names and initials of the patient(s) will not be published and due efforts will be made to conceal the identity, but anonymity cannot be guaranteed.

Data availability statement

All data generated or analyzed during this study are included in this published article.

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Nil.

Conflicts of interest

The authors declare that there are no conflicts of interests of this paper.

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