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New onset of Myasthenia Gravis in Patients with COVID-19: is it Causal or Coincidental?

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Abstract **Case Report**

COVID-19 pandemic is caused by highly infectious SARS-CoV-2. Observational studies have documented several neurological complications or associations either during or after the COVID-19. Some of them, have reported some case reports regarding COVID-19 in patients with a known history of myasthenia gravis (MG) but new onset of autoimmune MG in patients with COVID-19 is scarcely reported. Here, we report two novel cases of new-onset autoimmune MG following COVID-19 and describe the clinical and paraclinical findings in the context of other scarce reported cases.

Keywords: SARS-COV2, COVID-19, Myasthenia gravis, neuromuscular disorders, evolution.

INTRODUCTION

COVID-19 pandemic is caused by highly infectious SARS-CoV-2. The most common manifestations were atypical pneumonia and respiratory complications. However, observational studies have documented several neurological complications or associations either during or after the COVID-19. There have been some case reports regarding COVID-19 in patients with a known history of myasthenia gravis (MG) but new onset of autoimmune MG in patients with COVID-19 is scarcely reported [1, 2]. Here, we report two novel cases of new-onset autoimmune MG following COVID-19 and describe the clinical and paraclinical findings in the context of other scarce reported cases.

CLINICAL OBSERVATIONS

We report two cases of new onset MG in patients with COVID-19 who were hospitalized in neurological department of Ibn Rochd Hospital University during the COVID-19 pandemic.

Case 1

40-year-old woman with no previous known medical conditions, who presented with a 7-day history of heaviness of the limbs, diarrhea, myalgia, fever and extreme fatigue. COVID-19 had been confirmed with positive reverse transcription-polymerase chain reaction (RT-PCR) assay on the nasopharyngeal swab. On neurological examination, she had tetraparesis with normal reflexes. She soon developed diplopia and left eyelid ptosis. Electromyography showed a significant decremental response to 3-hertz repetitive nerve stimulation of the following nerve-muscle pairs: facial nerve-nasalis, spinal accessory-trapezius and ulnar nerve-abductor digiti minimi bilaterally. Motor and sensory nerve conduction parametrs were normal. Her AChR-binding antibody was positive at 20,40nmol/l. Thyroid function tests were normal. A chest computed tomography (CT) scan showed a large anterior mediastinal mass measuring 37 × 26 mm consistent with a thymoma on pathological examination and the percentage of lung involvement at the chest CT was less than 5%. Based on the combination of findings from history, laboratory investigations, electrophysiological

investigations and pathological findings, patient was diagnosed with seropositive myasthenia gravis with thymoma. The patient was started gradually on pyridostigmine 60 mg until 4 tablets per day and she reported a subjective improvement in her diplopia and ptosis. She had a full recovery from COVID-19 symptoms then she had a thymectomy, she is actually on chemotherapy for her thymoma.

Case 2

A previously well 25-year-old woman presented with a 10-day history of fever, cough, extreme fatigue, headaches and nasal voice. COVID-19 was confirmed by (RT-PCR) assay on the nasopharyngeal swab. She was admitted to the intensive care unit for an acute respiratory distress. The percentage of lung involvement at the chest CT was 20%. After the life-threatening state was averted and general condition improved, the patient kept limb heaviness, nasonate voice with onset of facial biparesia and dipolpia, she was transferred to our neurological department for investigation. On neurological examination, she had nasal intonation with normal visual acuity, ocular motility, pupillary size and reactivity, mild bifacial weakness. Motor and sensory examination, deep tendon reflexes, cerebellar and gait examination were normal. Electromyography showed a significant decremental response to 3-hertz repetitive nerve stimulation of the following nerve-muscle pairs: facial nerve-nasalis, spinal accessory-trapezius and ulnar nerve-abductor digiti minimi bilaterally. Her AChR-binding antibody were positive at 53,40 nmol/l. Thyroid function tests were normal. Based on the combination of findings from history, laboratory investigations and electroneurophysiological testing, she was diagnosed with seropositive myasthenia gravis. During the hospitalization the patient showed a progressive respiratory worsening, fever and dyspnea. A second chest-CT scan was performed and showed a bacterial superinfection but did not reveal any mediastinal mass. She received Ceftriaxone and Levofloxacin for two weeks and was treated by pyridostigmine 60 mg (4 tablets per day) with a significant improvement. After the infectious episode management, patient was started on 20mg of prednisone and gradually increased by 5mg every 3 days until the maximum level of 60 mg. The patient is scheduled for a thymectomy after stabilization.

Table-I: Summary of characteristics of our patients and literature

Authors	Age / gender	Comorbidities and family history	COVID symptoms	COVID Severity	CT chest	COVID-19 treatment	Duration between COVID-19	MG type	Thymus pathology	Antibody	MG Treatment	Outcome	Complications
Restivo *et al*[7]	64/M 68/M 71/F	None None None	Fever Fever Cough Fever	Mild Mild Severe	Normal Normal Bilateral Interstitil Pneumoia	NA NA Lopinavir/ritonavir HCQS	5 7 5	Generalised Generalised Generalised	None None None	AchR AchR AchR	PSL (75 mg/d); Pyridostigmine (240 mg/d) VIG (0.4/kg/d x 5 days) PLEX	Improved Improved Improved	None None None
Sriwastava *et al* [1]	65/F	Left RCC (S/P nephrectomy) Pituitary adenoma (S/P resection) Pulmonary Carcinoid Meningioma Old Pulmonary Embolism	Diarrhoea Myalgia	Severe	Bilateral Consolidation	Convalescent Plasma; Dexamethasone	11	Ocular symptoms only	None	AchR	Pyridostigmine (240 mg/d)	Improved	Septic Shock; Dysautonomia (Bradycardia)
Pérez Álvarez *et al*[8]	48/M	Paranoid Schizophrenia Inverse Psoriasis Positive ANA	Fever Cough Dyspnoea	Mild	Bilateral Consolidation	AZM; HCQS	15	Ocular symptoms only	None	AchR	NA	Improved	None
Huber *et al* [9]	21/F	Family history of hashimotos thyroiditis Addison's disease Pernicious anaemia	Cold Fatigue Anosmia Ageusia Diarrhoea	Mild	Normal	None	15	Ocular symptoms only	None	AchR	IVIG (0.4/kg/ day x 5 days); Pyridostigmine (180 mg/day)	Improved	None

Assini *et al* [10]	**77/M**	**None**	**Fever Dyspnoea**	**NA**	**Bilateral Interstitial Pneumonia**	**NA**	**56**	**Ocular symptoms only**	**None**	**MuSK**	**Pyridostigmine (240 mg/day) AZT (1.5 mg/kg)**	**Improved**	**None**
Muhammed *et al* [5]	24/F	None	Influenza like syndrome	Mild	NA	None	28	Generalised	None	MuSK	IVIG PSL (25 mg/day) Pyridostigmine	Improved	None
Muralidhar Reddy *et al*. [6]	65/M	Diabetes Hypertension	Fever, Cold and Cough	Mild	Normal	Remdesivir	42	Generalised	None	AchR	IVIG; PSL, AZT Pyridostigmine	Improved	None
Our cases	40/F 25/F	None None	diarrhea myalgia fever extreme fatigue fever cough extreme fatigue headaches	Mild Severe	Mediastinal Mass+ <5% of lung involvement 20% of lung involvement and a bacterial superinfection	AZM AZM	7 7	Generalised Generalised	thymoma None	AchR AchR	PSL Pyridostigmine thymectomy PSL AZT Pyridostigmine	Improved Improved	None acute respiratory distress

AchR: acetylcholine receptor antibody; ANA: antinuclear antibodies; AZM: Azithromycin; AZT: Azathioprine; F: female; HCQS: Hydroxychloroquine sulfate; IVIG : intravenous immunoglobulin; M: male; MuSK: muscle-specific kinase; NA: not available; PLEX : plasma exchange; PSL: prednisolone; RCC: Renal cell carcinoma

DISCUSSION

During the COVID-19 pandemic, it has been established those neurological complications in the form of autoimmune reactions, such as Guillain–Barré syndrome (GBS) and MG, may be provoked. Along with the patient's underlying predilection for the disease due to genetic factors, environmental factors may also play a role, further instigated by the viral infection [1]. There have been various case reports of COVID-19 infections in patients with pre-existing MG that have been published [2, 3]. There is only few reported cases in the literature with new onset MG following COVID-19 .In literature, clinical manifestations of new onset MG were generally mild and was due to antibody formation against the postsynaptic acetylcholine receptor and muscle specific kinase receptor [1,4-6]. To our knowledge, none of the patients in the literature had a thymoma. In our case report, we describe two novel cases of new onset MG concomitant to COVID- 19 infection who responded well to a standard dose of pyridostigmine and one of them with thymoma (Table I).

Some hypothetical explanations can be given for those newly onset cases of MG post-covid19.First, antibodies against SARS-CoV-2 might cross-react with AchR and MuSK receptors due to molecular mimicry between the viral proteins and the postsynaptic proteins. The latent period between the COVID-19 and MG favour this and disrupted self-tolerance. Second, COVID-19 produces a proinflammatory environment and cytokine storm leading to immune dysregulation been triggered by COVID-19 to become overtly symptomatic. Third, dormant MG might have hypothesis. Lastly, MG might be triggered by drugs like hydroxychloroquine sulfate and azithromycin prescribed often to treat COVID-19 which was not the case in our two patients [6].

CONCLUSION

Some infectious agents are known to be associated with MG, such as varicella zoster virus (VZV), West Nile virus (WNV), and Zika virus [1]. MG may be considered as neurological complication of infection with COVID-19. It is unclear whether COVID-19 could induce the production of antibodies against neuromuscular junctions triggering myasthenia gravis in COVID-19 patients. Longitudinal follow-up of such patients might provide additional insight into this unique link natural course of the disease.

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