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Rare Case of Late-onset Myasthenia Gravis in a 65-year-old Female with Prolonged Doxycycline Use

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Abstract

Myasthenia gravis (MG) is a rare autoimmune condition caused by antibody-mediated disruption of acetylcholine receptors (AChR) or their associated proteins. The age of onset of MG has a bimodal distribution, with a predominance of female cases in the second and third decades and a predominance of male cases in the sixth to eighth decades. MG is often unmasked by stressors such as systemic illness, medication, surgery, and pregnancy. We present a case of late-onset MG in a 65-year-old female with a recent history of prolonged doxycycline use. However, there are aspects of her past medical history, including comorbidities involving the immune system and numerous drug intolerances that should have increased clinical suspicion for MG. Additionally, one medical event that preceded symptom onset was pneumonia treated with doxycycline. This case suggests that doxycycline should be used with caution in MG patients, and that MG should be considered as part of the differential diagnosis in older female patients presenting with neurologic symptoms and suggestive past medical history.

Keywords

Myasthenia Gravis, Doxycycline

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Conflict of Interest Statement

The authors declare that they have no conflict of interest with this manuscript.

CASE REPORT

Rare Case of Late-Onset Myasthenia Gravis in a 65-Year-Old Female with Prolonged Doxycycline Use

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Abstract

Myasthenia gravis (MG) is a rare autoimmune condition caused by antibody-mediated disruption of acetylcholine receptors (AChR) or their associated proteins. The age of onset of MG has a bimodal distribution, with a predominance of female cases in the second and third decades and a predominance of male cases in the sixth to eighth decades. MG is often unmasked by stressors such as systemic illness, medication, surgery, and pregnancy. We present a case of late-onset MG in a 65-year-old female with a recent history of prolonged doxycycline use. However, there are aspects of her past medical history, including comorbidities involving the immune system and numerous drug intolerances that should have increased clinical suspicion for MG. Additionally, one medical event that preceded symptom onset was pneumonia treated with doxycycline. This case suggests that doxycycline should be used with caution in MG patients, and that MG should be considered as part of the differential diagnosis in older female patients presenting with neurologic symptoms and suggestive past medical history.

Keywords: Myasthenia gravis, Doxycycline

1. Introduction

Myasthenia Gravis (MG) is a rare neuromuscular autoimmune disorder caused by antibody binding to acetylcholine receptors (AChR) or its related proteins. MG has an annual incidence of 7–23 per million.¹ The age of onset has a bimodal distribution, with a predominance of female cases in the second and third decades and a predominance of male cases in the sixth to eighth decades.¹

MG is often unmasked by stressors such as systemic illness, medication, surgery, and pregnancy. Medications associated with unmasking or exacerbation of MG include aminoglycosides, fluoroquinolones, macrolides, beta blockers, magnesium, and quinine.² Of the antibiotics, gentamicin, tobramycin, ciprofloxacin, moxifloxacin, azithromycin, and clarithromycin are considered the highest risk based on incidence of adverse drug reaction reporting.³ How these compounds affect MG have yet to be elucidated, but existing studies suggest that aminoglycosides block

ACh release from the presynaptic membrane and fluoroquinolones affect AChRs on the postsynaptic membrane.⁴

MG has two clinical forms: ocular and generalized. In ocular MG, symptoms such as weakness are limited to the eyelids and extraocular muscles. In generalized MG, patients also have bulbar, limb, and respiratory weakness. Patients over the age of 50 are more likely to have ocular MG.⁶

Suspected cases of MG can be diagnosed at bedside with the ice pack test, which has a sensitivity of almost 80 percent.⁵ The ice pack test involves comparing the degree of ptosis before and after icing the eyelid for 2 min. Improvement in ptosis is considered a positive test, which can then be confirmed with serologic testing for autoantibodies.

2. Case presentation

A 65-year-old female with a past medical history of insulin-dependent diabetes, COPD requiring

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intermittent home oxygen, hypertension, hyperlipidemia, and CHF presented to the emergency department with ptosis, slurred speech, and dysphagia. These symptoms began one month before presentation with mild ptosis that gradually progressed to the point where the patient needed to tape her eyelids to her eyebrows in order to see and difficulty swallowing with the sensation of food stuck in her throat. Two weeks before presentation, her PCP recommended increasing oxygen use during meals, which mildly improved her dysphagia. She was also referred to and evaluated by ophthalmology, who reported no eyelid or intraocular abnormalities. One week before presentation, she developed slurred speech and reported occasionally saying incorrect words. She went to the ED at a different hospital, where she underwent stroke workup which was negative and was subsequently discharged. However, her symptoms persisted, which led her to present at our ED. Review of systems was positive for fatigue and decreased appetite.

Record review revealed a past medical history of allergic rhinitis, anxiety, asthma, atopic dermatitis, chronic pain, depression, and sinusitis. Records also indicated that three months prior to symptom onset, she had community acquired pneumonia and was prescribed six weeks of doxycycline, which she completed. Three weeks before admission, she was prescribed an additional three-week course of doxycycline, which she completed two days prior to presentation. Her other medications were insulin, ipratropium-albuterol, mometasone-formoterol, rosuvastatin, torsemide, valsartan, and albuterol. Her medical record also included numerous drug intolerances, including but not limited to aspirin, amoxicillin-clavulanate, budesonide, bupropion, cefditoren, ciprofloxacin, duloxetine, empagliflozin, fluticasone, flunisolide, gabapentin, glipizide, lisinopril, meloxicam, metoprolol, nitrofurantoin, paroxetine, pregabalin, semaglutide, tiotropium, and theophylline. She had a fifty-pack-year smoking history. Family history was unknown.

Physical examination revealed a patient appearing her stated age in no acute distress with bilateral facial drooping. She was alert and oriented, lung sounds were clear, heart was regular rate and rhythm with no murmurs, abdomen was soft, nontender and non-distended, extremities were warm and dry. On neurological exam she had slurred speech, dysphagia, bilateral ptosis worsened with sustained activity, incomplete eye closure, and weakness of bilateral upper and lower extremities, mainly in the proximal muscles. She had a positive ice-pack test. Vital signs were within normal limits.

EKG showed normal sinus rhythm. CXR and head CT showed no acute findings. Cardiac troponins, BNP, and TSH were within normal limits. The patient was admitted to the ICU for further monitoring of new or worsening neurologic symptoms.

On day 1 of her hospital admission, MRI of the brain and laboratory testing for AChR antibodies were ordered. On day 2, MRI was attempted but unable to be completed due to the patient's anxiety. Gastroenterology and neurology consults were placed, and monitoring was continued while awaiting consults (days 3 and 4).

On day 5, esophagogastroduodenoscopy was performed with results negative for esophageal strictures, neoplasia, and mucosal abnormalities. Thyroid ultrasound was negative for acute disease. She was seen by neurology, and due to high suspicion for MG, she was empirically started on Pyridostigmine 30 mg PO TID. Respiratory therapy checked her negative inspiratory force (NIF) BID to monitor for respiratory failure, but all values remained normal.

On day 6, she reported dramatic symptom improvement with normal speech and complete resolution of ptosis. She continued to have residual neck weakness, especially with periods of prolonged neck flexion. She was kept in the ICU for intubation in case of respiratory failure secondary to myasthenic crisis. Respiratory function was monitored with NIF measurements three times daily. On day 7, AChR antibodies returned positive, MG diagnosis was confirmed, and she was discharged home on 30 mg pyridostigmine TID.

3. Discussion

MG is more commonly diagnosed in men than women after age 50.⁷ As such, MG may be overlooked in a differential diagnosis for an older female, especially one with many comorbidities. In this case, the patient sought care for her symptoms multiple times before being evaluated for and diagnosed with MG. As hospitalists, we should keep MG in mind when evaluating muscle weakness, ptosis, and dysphagia in older women, especially since patients with late-onset MG are more likely to present with life-threatening events.⁶ Additionally, this patient presented with generalized MG, which is less common in her age group, but more likely to result in complications such as aspiration and respiratory failure.⁶

Another notable point is the prolonged use of PO doxycycline for pneumonia treatment. Though it cannot be confirmed, doxycycline may have been the unmasking agent in this patient's case as her

symptom onset coincided with her most recent course of doxycycline. It may be argued that the patient's MG was unmasked by her pneumonia or other systemic illnesses. However, in the last 5 years, she has had multiple pneumonias as well as hospitalizations for CHF and COPD, and she did not develop MG symptoms during those illnesses. Additionally, both the patient and her records indicated that her most recent pneumonia was not more severe than other past illnesses. Because of this, we believe it is more likely that doxycycline, rather than pneumonia, was the unmasking agent.

Interestingly, there have been two *in vitro* studies that have suggested a relationship between tetracyclines and MG. In one, researchers found that rolitetracycline depressed response to ACh stimulation in rat diaphragms.⁸ The other found that tetracycline inhibited nicotinic AChR channel currents in cell cultures.⁹

Despite these findings, there has only been one documented case of MG being unmasked by short term IV doxycycline, and tetracycline, doxycycline, and minocycline have not been associated with reported myasthenic drug reactions.³ Thus, this case could be considered a novel event of prolonged oral doxycycline unmasking MG. However, the criterion for defining an unmasking event remains unclear. Previous cases have reported unmasking occurring from a few hours to 6 weeks following exposure to an unmasking factor.^{10–13} As such, more research and community discussion are required to reach a consensus on what defines an unmasking event.

This case also raises possible indicators that should suggest MG as a possible diagnosis. Firstly, this patient had an extensive history of drug intolerances, including ciprofloxacin and metoprolol, which are known to unmask or exacerbate MG, as well as gabapentin and pregabalin, which have been implicated in MG exacerbations.^{4,14,15} Unfortunately, patient was unable to recall her reactions to these medications and these details were not in her medical record. Adverse reactions to drugs known to worsen MG could therefore be taken as a signal to suspect MG. Secondly, this patient had a history of asthma, atopic dermatitis, and allergies, which all involve an overactive immune system. These conditions have been associated with other autoimmune diseases,¹⁶ such as lupus,¹⁷ but to date have not been documented in conjunction with MG, suggesting a possible research area. Finally, this patient had anxiety and depression, which are mood disorder comorbidities that are associated with MG.¹⁸ Although individually these factors may not suggest MG as a possible diagnosis, if presented altogether they should increase clinical suspicion for MG.

4. Conclusion

Although MG is less prevalent in older female populations, this case illustrates the importance of keeping MG in mind as a potential diagnosis. This case also proposes doxycycline as a possible unmasking agent in MG, but highlights the gaps in our criteria for defining unmasking events. We suggest that prolonged courses of doxycycline be used with caution in MG. Additionally, key elements of this patient's history suggest possible indicators, specifically drug intolerances, other immune conditions, and mood disorders, that should raise suspicion for MG.

Conflict of interest

The authors declare that they have no conflict of interest with this manuscript.

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