ATYPICAL ANTIPSYCHOTIC DRUG UNMASKING MYASTHENIA GRAVIS IN THE FORM OF MYASTHENIA CRISIS: A CASE REPORT

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ABSTRACT

Myasthenia gravis (MG) is the most common autoimmune disorder of the neuromuscular junction (NMJ). The clinical presentation of myasthenia gravis can range from mild ptosis to myasthenia crisis. A myasthenic crisis is characterized by respiratory failure secondary to respiratory or oropharyngeal muscle weakness requiring ventilatory support. Despite well healthcare access, 20% of patients still have myasthenia crisis as the first presentation of the disease. The diagnostic delay in myasthenia gravis can result in increase in the morbidity and mortality. We report a case of a 22-year-old female initially misdiagnosed with moderate depression for six months after the onset of symptoms and was treated with antipsychotics. Six months after this regimen precipitated the disease, she presented with acute respiratory failure and was diagnosed as myasthenia crisis. Laboratory test confirmed an elevated anti-AChR antibody level. The patient was treated with intravenous immunoglobulin (IVIG), corticosteroids, and anticholinesterase medication, resulting in significant recovery.

KEYWORDS

Myasthenia crisis, Antipsychotics, Haloperidol, Risperidone

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INTRODUCTION

Myasthenia gravis (MG) is an immune mediated syndrome caused by impaired neuromuscular transmission. It results from binding of autoantibodies to proteins at the neuromuscular junction (NMJ) which includes the nicotinic acetylcholine receptor (AChR), muscle-specific tyrosine kinase (MuSK) involved in AChR, lipoprotein-related protein 4 (LRP4) or agrin in the postsynaptic membrane at the neuromuscular junction. This results in reduced number and density of AChR-endings with abnormal transmission across the neuromuscular junction and clinically presents as muscle weakness. MG has a bimodal peak of incidence, with the first peak in the third decade of life, which commonly affects females and the second peak in the sixth and seventh decades affecting males.[1] Pyridostigmine is the first line symptomatic treatment, and for unresponsive patients, corticosteroids, azathioprine, and thymectomy are available treatment options. Severe respiratory muscle weakness with consequent respiratory failure is reported in approximately 15% of MG patients, and this is known as a myasthenic crisis (MC), which is considered a neurological emergency that necessitates immediate action and admission to the intensive care unit.[2] Interestingly, MC could be the initial manifestation during surgery, infection, drugs, stress, pregnancy, and the postpartum period. Patients with an underlying myasthenic condition typically experience temporary worsening of symptoms when taking certain medications, such as different antibiotics or cardiovascular drugs (beta blockers, calcium channel blockers), which directly impair neuromuscular transmission due to different pre- or postsynaptic or combined mechanisms. In these situations, discontinuation of myasthenia-aggravating medications is beneficial. Certain medications (such as d-penicillamine and immune checkpoint inhibitors) or therapies (such as allogeneic stem cell transplantation) have the potential to cause de novo myasthenic syndromes. In these situations, discontinuing medication alone might not be sufficient to alleviate the symptoms.[3] Additionally, antipsychotics have an established effect on myasthenia gravis exacerbation; these medications impair neuromuscular transmission at the postsynaptic membrane and inhibit ACh release from the presynaptic membranea.[4] A similar dose-dependent mechanism was documented with the use of atypical antipsychotics such as clozapine, olanzapine, sulpiride, and risperidone, and haloperidol has also been reported to cause deterioration of symptoms in myasthenia cases.[5] This case report discusses the implications of psychiatric medication in precipitating MC and emphasizes the importance of accurate diagnosis and careful medication management in patients with MG.

CASE REPORT

A 22-year-female presented to the emergency department with sudden onset of breathlessness and cough. Her Glasgow Coma Scale score was E2V1M3. Her blood pressure was 110/70 mm of Hg, pulse rate was 124 beats/min and was afebrile. She had shallow breathing with poor respiratory effort and a respiratory rate of 8 breaths per minute. The oxygen saturation was 86% on facemask with the reservoir at 9-10 L/min oxygen flow. The patient had normal systemic examination findings with bilateral reactive pupils, clear chest, no murmurs, and normal reflexes with no evidence of focal neurological deficits. Her medical history revealed that she had been symptomatic for the last two years with symptoms of bilateral lower limb weakness, easy fatiguability, low mood, and lack of energy. Six months before her symptoms worsened, with the development of right eye ptosis, impaired speech, difficulty in swallowing, and drooling of saliva. She had multiple hospital visits for her symptoms and had received treatments such as calcium and vitamin supplements. With no improvement in her symptoms, she was reassured and referred to a psychiatrist, where she was diagnosed as moderate depression with psychotic features and was prescribed antidepressants and antipsychotics. The starting regimen of her psychiatric treatment was oral sertraline (25 mg/day) and haloperidol (1 mg/day), and the patient was advised monthly follow-up. After two months, the drugs were titrated to tablet sertraline 50 mg once daily and tablet haloperidol 2 mg/day in two divided doses. Despite increasing the dose, her symptoms persisted, and oral risperidone was added to the above regimen at a dose of 0.5 mg/day on her third follow-up visit to the psychiatrist. Six months after starting antipsychotic medications, the patient came to our emergency department with respiratory failure. Her blood test results were normal; however, arterial blood gas analysis revealed a PH of 7.1, PO2 of 32 mmHg, and PCO2= 104.2 mm of Hg. With a high clinical suspicion of MC, the patient was urgently intubated for airway protection and mechanical ventilation. She was placed on pressure support ventilation with the following settings: tidal volume 8 mL/kg body weight i:e; (≈440 mL), pressure support 12 cmH_2O, positive end-expiratory pressure (PEEP) 5 cmH_2O, fraction of inspired oxygen (FiO_2) 40%, and an inspiratory-to-expiratory (I:E) ratio of 1:2. Blood samples for laboratory testing of anti-AChE antibody levels were sent and the results were expected to come after four days. Based on the preceding history of drug intake for neuropsychiatric illness followed by an exacerbation of her muscle weakness, we started the patient on intravenous human immunoglobulin (IVIG) at a dose of 2g/kg daily divided dose for five days (total cumulative dose: 110 gm). On the second day, corticosteroids (40 mg of prednisolone tablet once daily via an NG tube) was administered. Improvement in the strength of the neck flexors and other adjunct muscles was used as a guide to assess improvement in respiratory and bulbar muscle function. On the third day, the patient was transitioned to a spontaneous mode of ventilation, in which all breaths were self-initiated. The ventilator pressure settings were gradually reduced to a minimum and the patient was extubated. The anti-AChE antibody level was 0.8 nmol/L (standard value <0.40 nmol/L). Accordingly, all antipsychotic and antidepressant medications were discontinued, and she was discharged on oral pyridostigmine 30 mg four times daily and oral prednisolone 30 mg once daily.

DISCUSSION

Myasthenia gravis is an autoimmune disorder with a hallmark clinical manifestation of muscle weakness that worsens with exertion and improves with resting.[6] The most common precipitant is infection. A study has documented infection in 38% of patients presenting with myasthenic crisis, most commonly bacterial pneumonia. Other precipitants had aspiration pneumonitis, surgery, pregnancy, perimenstrual state, certain medications, and tapering of immune- modulating medications.[7] Numerous medications may exacerbate MG, including quinidine, procainamide, beta-adrenergic antagonists, calcium channel antagonists (verapamil, nifedipine, and felodipine), magnesium,

antibiotics (ampicillin, gentamicin, streptomycin, polymyxin, ciprofloxacin, and erythromycin), phenytoin, gabapentin, methimazole, α-interferon, and contrast media. These medications should be used cautiously in patients with myasthenia, particularly after surgery. Any medication suspected of precipitating myasthenic crisis should be discontinued.[8] In this report, we described a case of myasthenia gravis with an initial presentation of neuropsychiatric manifestations. The preceding history of low mood and easy fatiguability with no suggestive clinical findings on systemic examination obscured the suspicion of myasthenia gravis and caused an unnecessary diagnostic delay. In the present case, we believe that the precipitating factor for the crisis episode was antipsychotic medication intake. Our patient was taking an antidepressant drug sertraline, a finding that is consistent with a study conducted by Trillenberg et al which showed that sertraline has a high odds ratio of precipitating an event of myasthenia crisis.[9] However, not all psychiatric drugs precipitate a myasthenia crisis. In a study conducted by Berthet et al, patients with myasthenia were treated with antipsychotic medications, namely haloperidol and risperidone, with no exacerbation of symptoms.[10] Furthermore, neuroleptics are not mentioned in the list of drugs to be avoided in the management recommendations of the myasthenia gravis.[8] The limitation of our study is the long latency period of six months between the start of antidepressant medication and an event of myasthenia crisis.

CONCLUSION

Various drugs are known for their adverse effects on myasthenia gravis through different mechanisms, including myasthenia gravis-like symptoms, unmasking myasthenia gravis, precipitating myasthenia gravis, or de novo myasthenia gravis induction. Diagnostic delay in myasthenia gravis patients by physicians and neurologists can bring the patient to a state of life-threatening respiratory failure. Hence, a high index of suspicion is needed whenever a patient complains of fatigability, generalized weakness, and related symptoms.

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CONFLICT OF INTEREST

None

AUTHORS CONTRIBUTION

Manoj Karki was involved in conceptualizing, writing and proofreading the study; Subodh Bashyal was involved in writing and proofreading the study; Sudhan Devkota, Aparajita Sharma and Bidhata Rayamajhi were involved in patient care and proofreading; Niraj Kumar Jaiswal guided throughout the study approved and finalized the manuscript.

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