Case in Point

Diltiazem Exacerbated Myasthenia Gravis

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Although this patient's symptoms mimicked those he had experienced 10 years earlier, it was difficult for clinicians to identify the cause.

Myasthenia gravis (MG) is an autoimmune disorder characterized by involuntary muscle weakness and fatigue. It usually begins with the extraocular muscles and eventually descends to bulbar muscles involving the jaw, neck, proximal limbs, and respiratory muscles. The most common symptoms include ptosis, dyspnea, dysarthria, diplopia, and difficulty speaking or swallowing.[1] Although the exact mechanism of MG is not fully understood, the role of antibody-mediated pathogenesis at the neuromuscular junction level has been well established. In MG, antibodies are directed against postsynaptic nicotinic acetylcholine receptors (AChRs), causing impairment of neuromuscular transmission. However, AChR antibody levels may not be detectable in about 15% of patients with generalized MG, indicating that other mechanisms may be contributing to the condition.[2]

The prevalence of the disease is about 1 in 10,000 to 50,000 of the population. In the United States, it is estimated that about 100,000 people have been diagnosed with MG in 2006. The hallmark of this disease is the erratic exacerbations and remissions, and in some situations this could lead to life-threatening myasthenic crises during the early phase.[2] As of today, general guidelines for the treatment of MG remain unavailable; however, first-line therapy generally is acetylcholinesterase inhibitors for symptomatic treatments. Other therapies include immunosuppression with glucocorticoids, plasmapheresis, intravenous immune globulin (IVIG) and thymectomy.[1]

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CASE REPORT

A 53-year-old white man underwent a thymectomy and started on prednisone and pyridostigmine after being diagnosed with MG by electromyography at age 31 years. Symptoms of dysarthria, general fatigue, and gradual onset of diplopia started 2 years prior to diagnosis. The patient experienced difficulty holding his arms over his head while washing his hair and began noticing some difficulty climbing stairs with intermittent diplopia. These symptoms continued at a mild level for the next 3 to 4 months. The patient also noticed occasional ptosis that started on the left eyelid and progressed to the right eye at the end of the day, which led him to seek medical care.

MG was the primary consideration during his first neurology appointment when the patient was noted to have dysconjugate gaze secondary to right intranuclear ophthalmoplegia and bilateral sixth nerve palsies. Other differential diagnoses also considered at this evaluation included multiple sclerosis or ischemic disease.

Over an 8-year period, the patient continued to have frequent episodes of increased weakness, diplopia, and shortness of breath requiring regular use of IVIG and high-dose courses of prednisone. He was also found to have a recurrent thymoma on a chest computed tomography (CT) scan and underwent a second thymectomy at age 41 years, which drastically improved his symptoms. He still noted occasional mild dysarthria late in the day, but remained otherwise stable on his maintenance dose of prednisone 20 mg every other day, pyridostigmine 60 mg 3 to 4 times per day as needed, and azathioprine 150 mg every morning and 100 mg every night.

The patient remained stable until his antihypertensive medication was switched by a psychiatry nurse practitioner from losartan 100 mg daily to metoprolol tartrate 25 mg twice daily due to uncontrolled hypertension and tachycardia in October 2008. Three months later, the patient followed up with his primary care provider with complaints of shortness of breath and unusual sudden jerking of the legs when falling asleep. Metoprolol tar-

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trate was switched to diltiazem SA 120 mg daily at this visit due to the patient's history of asthma and chronic obstructive pulmonary disease.

In March 2009, 2 months after starting diltiazem, the patient was found to have shortness of breath, diffuse malaise, and uncontrollable body twitches. On admission, he exhibited mild left ptosis, dyspnea, dysphagia, and worsened generalized muscle weakness compared to baseline. His pulse was 104 beats per minute, blood pressure was 139/96 mm Hg, respiratory rate was 22 per minute, and temperature was 97.9°F. Upon physical examinations, respiratory system revealed loss of breath sounds in the right lower lung field.

Central nervous system examination was normal except for muscle twitching disrupting the patient's sleep with right hemi-diaphragm elevated due to phrenic nerve (C3-C5) damage from past thymectomies. Otherwise, cardiovascular, gastrointestinal, and neurologic systems were clinically normal. Laboratory studies showed electrocardiography; brain natriuretic peptide; troponin; serum creatinine and electrolytes; urinary analysis; hemoglobin A1C level; international normalized ratio; and thyroid-stimulating hormone values were within normal limits except for elevated hemoglobin of 18 g/dL, hematocrit 52.3%, and D-dimer of 637 ng/mL fibrinogen equivalent units.

Further investigation revealed that the patient was hospitalized at another institution for similar symptoms: shortness of breath, generalized weakness, and body twitches. The patient confirmed that symptoms were comparable to MG exacerbations he had more than 10 years ago. He had completed a 5-day course of IVIG 45 g daily infusions as recommended by a neurologist 2 weeks prior to this admission. He reported that symptoms improved and gradually returned about 5 days after stopping IVIG infusion from the previous admission.

Due to the extensiveness of his symptoms and recent hospitalization, the patient was admitted to the internal medicine floor for further evaluation. He was started on IVIG 45 g infusion and prednisone 20 mg daily. The patient reported shortness of breath and that generalized muscle weakness worsened since starting diltiazem, which was immediately discontinued. Lisinopril 20 mg and hydrochlorothiazide 12.5 mg daily were substituted for blood pressure control. Patient's respiratory function, body twitches, and diffuse malaise significantly improved within 48 hours of stopping diltiazem. On day 3, the patient's generalized muscle weakness was found to return to baseline. He completed his 5-day course of IVIG and was discharged with no further complaints of generalized fatigue and shortness of breath. When followed up in the outpatient neurology clinic 3 weeks later, he was found to be clinically stable with good blood pressure of 134/86 mm Hg and heart rate of 78 beats per minute.

DISCUSSION

A few clinical observations indicated that calcium channel blockers, and other medications, may adversely affect neuromuscular transmission.[3-5] However, many health care providers are still unfamiliar with these disease-drug interactions as demonstrated in the case above. Our patient was clinically stabilized on an MG regimen for more than 10 years until diltiazem was introduced to control his blood pressure. The patient recovered well after discontinuation of diltiazem. The exact mechanism of calcium channel blockers in relation to neuromuscular junction blockade is not well understood. However, selected calcium antagonists, including verapamil, nifedipine, and felodipine have been documented to increase weakness and respiratory failure in patients with MG.[3-5]

We concluded that diltiazem was the cause that led to an exacerbation of this patient's stabilized MG condition. To our knowledge, this is the first case report of diltiazem-exacerbated MG. Although further research and studies are needed to determine if non-dihydropyridine and dihydropyridine calcium channel blockers would affect MG patients at the same severity, we recommend that all calcium channel blockers should be avoided in patients with this disorder. ●

Author disclosures

The authors report no actual or potential conflicts of interest with regard to this article.

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