

Severe Progressive Weakness in a 58-Year-Old Man

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Myasthenia gravis historically has been associated with significant morbidity and mortality rates, and most of those afflicted either died of the disease or became greatly disabled. However, modern understanding of the pathogenesis of this disorder has led to several effective treatments which have transformed the prognosis of this disease greatly.

A 58 year-old man presented to our facility complaining of a one-week history of increasing difficulty in "holding his head up." About eight months earlier, he had begun to experience generalized muscle weakness, which worsened in the evenings. This weakness progressed gradually until ambulation and activities of daily life became difficult. He could not even hold his head up without the use of a cervical collar (Figure 1). In addition, he complained of some difficulty with breathing and swallowing. He also reported a forty-pound weight loss over the preceding year. He

denied fevers, chills, or malaise, and his symptoms were not associated with any pain, fatigue, sleepiness, cold intolerance, depression, orthopnea, or paroxysmal nocturnal dyspnea.

His past medical history was significant for hypothyroidism diagnosed one year earlier and congestive heart failure diagnosed 4 months earlier. His medications included lisinopril, furosemide, digoxin, spironolactone, levothyroxine, and aspirin. With the exception of the levothyroxine, the patient was taking these medications as prescribed. He was allergic to penicillin and sulfa-

CME INFORMATION

TARGET AUDIENCE

The November/December Clinical Case of the Month is intended for family physicians, general internists, general practitioners, emergency medicine physicians, pediatricians, radiologists, and neurologists.

EDUCATIONAL OBJECTIVES

The Clinical Case of the Month is a regular educational feature presented by the Louisiana State University Department of Medicine in New Orleans. Medical students, residents, postdoctoral fellows, and faculty collaborate in the preparation of these discussions. After reading this article, physicians should be able to better identify and understand the pathophysiology, clinical presentation, diagnosis, and treatment of myasthenia gravis.

CREDIT

The LSMS Educational and Research Foundation des-

ignates this educational activity for a maximum of one (1) hour of category 1 credit toward the AMA Physician's Recognition Award. Each physician should claim only those hours of credit that he/she actually spent in the educational activity.

DISCLOSURE

Dr. Sondes has nothing to disclose.
Dr. Kennedy has nothing to disclose.
Dr. Kishner has nothing to disclose.
Dr. Lopez discloses that he is a member of the LSMS *Journal* Board and the LSMS *Journal* Editorial Board.
Dr. Anthony has nothing to disclose.

Original Release Date

12/31/2002

Expiration Date

12/31/2003

Estimated time to complete this activity is 1 hour.

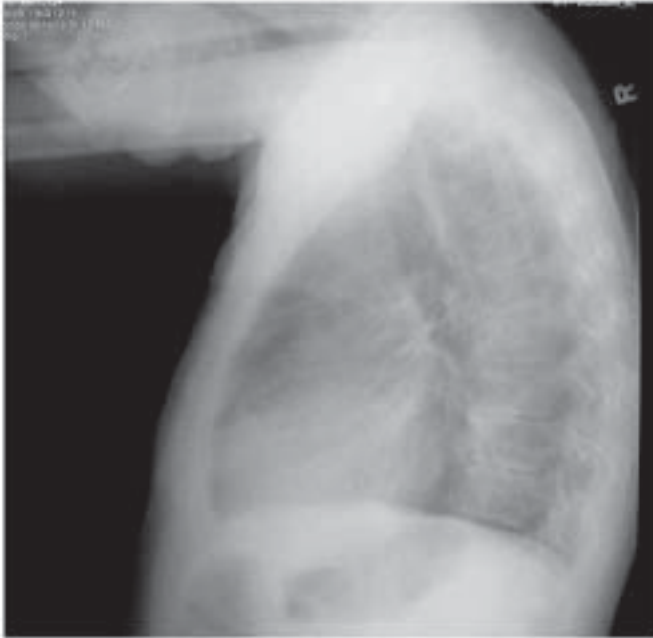


Figure 1. Lateral view of chest and neck demonstrating profound cervical weakness.

based medications. The patient's mother had a history of unspecified "thyroid problems". He denied any history of heavy alcohol use, illicit drug use, and had stopped smoking cigarettes ten years previously.

On physical exam, he was alert and oriented but in mild respiratory distress. His vital signs were: temperature 36.6° C, pulse 119 beats per minute, respirations of 28 per minute, blood pressure of 128/69, and an oxygen saturation of 97% in ambient air. Cardiovascular examination revealed mild tachycardia without gallop(s) or murmur. Lungs were clear to auscultation bilaterally. The neurological exam was notable for mild bilateral ptosis, and motor strength of 4/5 in the extremities, but only 2/5 with neck extension. Reflexes and cerebellar function were normal. The remainder of the physical exam was unremarkable.

Significant lab values included a hemoglobin of 10.4 g/dL (normal 14.0-18.0 g/dL) with a normal mean cell volume, thyroid stimulating hormone of 9.19 ug/dL (normal 0.5-5.0 ug/dL), and arterial blood gas pH of 7.43 (normal 7.35-7.45), pCO₂ of 53 mmHg (normal 35-45), pO₂ of 63 mmHg (normal >90), and bicarbonate of 30 mEq/L (normal 24-30).

After admission, an edrophonium test was performed in order to assess for myasthenia gravis. Ten milligrams of edrophonium were injected, and the patient reported a dramatic subjective improvement of his respiratory difficulty though minimal to no objective improvements in muscle strength elsewhere were appreciated.

On the fifth hospital day, the patient underwent nerve conduction studies (NCS) and electromyography (EMG) in order to better elucidate the cause of weakness. Pyridostigmine, which the patient had been taking for several days, was stopped 18 hours prior to NCS/EMG. During NCS/EMG, the patient was evaluated for polyneuropathy and polyradiculopathy. These tests were negative. Additional EMG testing also ruled out a myopathy as another possible cause of weakness, a concern because of the patient's history of hypothyroidism and elevated serum level of thyroid stimulating hormone. Lastly, repetitive stimulation at 3Hz was performed on the right abductor digiti minimi (ADM) and the left obicularis oculi (OBO). Testing showed an 11% decrement in the amplitude of the motor unit action potential (MUAP) after repetitive stimulation of the right ADM and a 33% decrement in the amplitude of the MUAP after stimulation of the OBO. Both of these findings were electrophysiologically consistent with myasthenia gravis. Pyridostigmine without steroids was continued, and the patient experienced marked improvement in the strength of all affected muscles in the following week. Antibodies to acetylcholine were not drawn due to the positive EMG/NCS findings and the improvement in symptoms after pyridostigmine was started. His other medications including levothyroxine were continued. At follow-up appointments 1 month and 3 months after discharge, the patient's symptoms of dysphagia and weakness had completely resolved.

DISCUSSION

Myasthenia gravis affects approximately 1 in 25,000 persons in the United States and may present at any age, although usually in women of child-bearing age and men greater than 60 years of age.¹ Patients characteristically develop rapid fatigability of the skeletal muscles, which improves with rest. Most patients experience weakness of extraocular and eyelid muscles early in the course of the illness and in approximately 15% of patients the weakness remains localized to these areas, resulting in ptosis and diplopia². The bulbar muscles may also be affected, causing difficulty in swallowing and nasal speech. Approximately 85% of patients will develop more generalized muscle weakness. This weakness is usually most pronounced in the proximal muscles and neck extensors, as was the case in our patient. The muscles of respiration can also be severely affected, and the patient may require mechanical ventilation and monitoring in an ICU. Of note, the physical exam should demonstrate a complete lack of involvement of the sensory nerves; reflexes and proprioception should also be normal. In addition, the intensity of symptoms in this disease frequently fluctu-

ates creating an almost diurnal pattern.

Myasthenia gravis is an autoimmune disorder in which an autoantibody is directed against the nicotinic acetylcholine receptor. By a number of different mechanisms, these antibodies decrease the effective number of acetylcholine receptors, resulting in decreased numbers of contractions of individual muscle fibers.³ Even though the pathogenesis of disease is relatively well-understood, little is known about what actually precipitates the cascade of immune-associated events. Recent research suggests a possible role of molecular mimicry in which exposure to microbial antigens induces the production of antibodies which cross-react with various epitopes located on the acetylcholine receptor.⁴ Such research may lead to the development of molecularly-targeted therapies that block specific steps in the presentation of MHC class II molecules to T-cells that initiate immune responses.

The diagnosis of myasthenia gravis is primarily clinical and suggested by the history and physical examination findings. However, several tests can be helpful in diagnosing myasthenia gravis. The Tensilon test involves administering a short-acting, acetylcholinesterase inhibitor, edrophonium chloride. This leads to a transient, often dramatic, relief of symptoms in approximately 80% of patients with myasthenia gravis. However, false positives and false negatives have been known to occur, and in the presence of an equivocal test, additional evidence of disease is needed before potentially harmful therapies are initiated⁵.

The ability to detect acetylcholine receptor antibodies has greatly assisted in the diagnosis of myasthenia gravis. Eighty percent to ninety percent of patients with myasthenia gravis will test positive by radioimmunoassay for the presence of acetylcholine receptor antibodies in the serum.⁶ Of the approximately 15% of patients in which the antibody is not found, experiments have shown that when their immunoglobulin is transferred to mice, a similar neuromuscular defect occurs.⁷ These patients have disease which is indistinguishable from that of antibody-positive myasthenia gravis. Recent discoveries have shown that the majority of these patients produce antibodies to a tyrosine kinase specific to muscle cells.⁸ These antibodies are believed to interfere with a pathway crucial to normal function at the neuromuscular junction.

The diagnosis of neuromuscular transmission disturbances consistent with myasthenia gravis can also be made with the use of EMG/NCS. The neuromuscular junction in suspected myasthenia gravis is best studied by repetitive nerve stimulation. Under normal conditions, repetitive nerve stimulation will not produce a detectable abnormality. With myasthenia gravis, however, repetitive nerve stimulation can result in record-

able neuromuscular transmission abnormalities. In myasthenia gravis there is a post-synaptic neuromuscular junction defect due to acetylcholine receptor antibodies. This leads to a reduction in the number of potential acetylcholine interactions thereby reducing the safety margin normally present in neuromuscular transmission. Once the nerve being tested is repetitively stimulated in a myasthenia gravis patient, a decrement in the amplitude of the compound motor action potential may be noted (typically >10% by the fourth action potential) due to the reduction of available acetylcholine receptors.

TREATMENT

Modern treatments of myasthenia gravis have transformed this previously grave disease into an illness that can usually be controlled and allow afflicted individuals to lead essentially normal lives. The mainstay of symptomatic therapy for mild-to-moderate disease is an acetylcholinesterase inhibitor like pyridostigmine. Side-effects of these medications include muscle fasciculations, abdominal cramping, diarrhea, and weakness. Immunosuppressive therapy with corticosteroids (ie, prednisone) is necessary in those more severely affected and those not optimally controlled with acetylcholinesterase blocking agents. Other immunosuppressive agents such as azathioprine and cyclosporine can be used as steroid-sparing agents. Severe or refractory cases may be treated with plasmapheresis or intravenous immune globulin.

Mention should also be made of surgical treatment of myasthenia gravis with thymectomy. Regardless of whether or not the patient has a co-existent thymoma, removal of the thymus gland is often associated with improvement of symptoms. Nearly all patients with generalized myasthenia gravis who are between puberty and approximately 60 years of age should be considered for thymectomy. A retrospective Mayo Clinic study comparing groups of patients with or without thymectomy showed that 85% of patients who underwent thymectomy experienced either a remission or at least improvement in symptoms.⁹ This result was significantly better than in those individuals who did not undergo thymectomy.

SUMMARY

Myasthenia gravis is an autoimmune post-synaptic neuromuscular junction disorder that is usually identified clinically. Assistance with the diagnosis can be pursued with edrophonium chloride administration (ie, Tensilon test), electromyography with repetitive nerve stimulation, and serologic testing for acetylcholine receptor antibodies. Medical and surgical treatments can poten-

tially improve the symptoms and outcome of those affected by myasthenia gravis. When confronted with a patient with weakness made worse by fatigue, myasthenia gravis should always be included in the differential diagnosis.

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CME QUESTIONS

To earn CME credit, read the preceding CME article and complete the registration, evaluation, and answer form on page 335. Mail or fax the registration, evaluation, and answer form to the Educational and Research Foundation. Answers must be postmarked or faxed prior to December 31, 2003. Participants must attain a minimum score of 75% to receive credit.

For each question, choose the one answer that is most correct.

1. All of the following statements are true regarding myasthenia gravis except:
 - a) Myasthenia gravis affects approximately 1 in 25,000 persons in the United States.
 - b) Myasthenia gravis may present at any age, although usually in younger women and men greater than 60 years of age.
 - c) Patients characteristically develop rapid fatigability of the skeletal muscles which improves with exercise.
 - d) Most patients experience weakness of extraocular and eyelid muscles early in the course of the illness.
2. True or False. In myasthenia gravis, the physical exam typically reveals marked abnormalities in sensation, reflexes, and proprioception.
3. Myasthenia gravis is an autoimmune disorder in which an autoantibody is directed against the:
 - a) Acetylcholine receptors
 - b) White matter of the brain
 - c) Facial nerve
 - d) Benzodiazepine receptors
4. Treatment options for patients with myasthenia gravis include all of the following except:
 - a) Steroids.
 - b) Thymectomy.
 - c) Imipenem.
 - d) Acetylcholinesterase inhibitor.
 - e) Plasmapheresis.