

# Severe Asthma Associated With Myasthenia Gravis and Upper Airway Obstruction

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## ■ Abstract

An unusual association of asthma and myasthenia gravis (MG) complicated by tracheal stenosis is reported. The patient was a 35-year-old black woman with a history of severe asthma and rhinitis over 30 years. A respiratory tract infection triggered a life-threatening asthma attack whose treatment required orotracheal intubation and mechanical ventilatory support. A few weeks later, tracheal stenosis was diagnosed. Clinical manifestations of MG presented 3 years after her near-fatal asthma attack. Spirometry showed severe obstruction with no response after inhalation of 400 µg of albuterol. Baseline lung function parameters were forced vital capacity, 3.29 L (105% predicted); forced expiratory volume in 1 second (FEV<sub>1</sub>), 1.10 L (41% predicted); maximal midexpiratory flow rate, 0.81 L/min (26% predicted). FEV<sub>1</sub> after administration of albuterol was 0.87 L (32% predicted). The patient's flow–volume loops showed flattened inspiratory and expiratory limbs, consistent with fixed extrathoracic airway obstruction. Chest computed tomography scans showed severe concentric reduction of the lumen of the upper thoracic trachea.

Key words: Asthma. Tracheal stenosis. Myasthenia gravis. Exacerbation.

## ■ Resumen

En este caso informamos de una asociación infrecuente entre el asma y la miastenia grave (MG) complicada por estenosis traqueal. La paciente era una mujer negra de 35 años de edad con un historial de asma grave y de rinitis durante más de 30 años. Una infección de las vías respiratorias provocó un ataque de asma potencialmente mortal para cuyo tratamiento fue necesario realizar una intubación orotraqueal y proporcionar respiración asistida. Unas semanas más tarde, se le diagnosticó estenosis traqueal. Las manifestaciones clínicas de la MG aparecieron tres años después del ataque de asma casi mortal. La espirometría reveló una obstrucción grave sin respuesta a la inhalación de 400 µg de salbutamol. Los parámetros de referencia de la función pulmonar fueron los siguientes: capacidad vital forzada 3,29 L (105% del valor teórico); volumen espiratorio forzado en el primer segundo (FEV<sub>1</sub>), 1,10 L (41% del valor teórico); flujo máximo mesoespiratorio, 0,81 L/min (26% del valor teórico). El FEV<sub>1</sub> tras la administración del salbutamol fue de 0,87 L (32% del valor teórico). Las curvas de flujo–volumen de la paciente revelaron ramas inspiratorias y espiratorias planas, sugerentes de obstrucción de las vías respiratorias extratorácica fija. Las tomografías axiales computerizadas del tórax revelaron una grave reducción concéntrica de la luz de la tráquea torácica superior.

Palabras clave: Asma. Tráquea. Estenosis. Miastenia Grave. Reagudización.

## Introduction

Asthma is a highly prevalent disease characterized by chronic airflow limitation that reverses spontaneously or after bronchodilator use. From an immunological standpoint, allergic asthma is characterized by a type 2 helper T cell (T<sub>H</sub>2) cytokine profile, elevated levels of interleukin (IL) 4 and IL-

5, immunoglobulin (Ig) E production, and activation of mast cells and basophils.

Myasthenia gravis (MG) is an acquired autoimmune disorder of the postsynaptic neuromuscular junction caused by antibodies directed against the acetylcholine receptor (AChR) [1]. In addition, overexpression of CD23 (the low affinity receptor for IgE) in the germinal centers of the

thymus of MG patients has been reported [2]. That molecule seems to be involved in various allergic diseases as well as in MG. It has also been reported that Churg–Strauss syndrome, allergic myelitis and other autoimmune disorders such as hypothyroidism and inflammatory bowel disease are associated with allergic diseases and respiratory symptoms [3]. Both asthma and MG can exacerbate and in some circumstances become life threatening, requiring hospitalization, intensive care, and mechanical ventilatory support.

In this report, the authors describe a patient with asthma associated with MG and tracheal stenosis.

## Case Description

A 35-year-old black woman with a history of asthma and allergic rhinitis described asthmatic symptoms such as dyspnea and wheezing starting when she was 5 years old and becoming more intense and frequent over the years. Nasal blockage and itching were associated with the asthmatic complaints. She was taking inhaled corticosteroids and used  $\beta_2$ -agonists as rescue medications with poor control of her symptoms.

In 1999, she had a severe asthma crisis just after a respiratory infection and required hospitalization, orotracheal intubation, and mechanical ventilatory support for 7 days. Labored breathing, dysphonia, and rough tracheal sounds appeared a few weeks after hospital discharge. An ear-nose-and-throat physician diagnosed a narrowing of the upper third of her thoracic trachea. In 2002, she presented with diplopia, ptosis, and difficulty both swallowing and speaking; a neurologist diagnosed MG. An electromyogram showed a weakly reduced response to repetitive nerve stimulation. She had no family history of MG or asthma, although her father had allergic rhinitis. Treatment with prednisone was initiated. Azathioprine was added later.

In 2005, she visited our outpatient clinic specialized in asthma and allergic rhinitis. She complained of dyspnea, physical activity limitation, and daily asthma symptoms, nocturnal awaking twice a week, and heartburn. Physical examination revealed mild cushingoid facies, a body mass index of 29.3, and a heart rate of 89 beats/min. Blood pressure was normal. Neck auscultation revealed a loud, strident biphasic respiratory sound (stridor). Lung auscultation revealed a slight, bilateral murmur without wheezing. No arrhythmias or any other abnormal heart sounds were detected. A complete neurological exam revealed no abnormalities.

Spirometry showed severe obstruction with no response after administration of 400  $\mu$ g of inhaled albuterol. Lung function parameters at rest were forced vital capacity (FVC), 3.29 L (105% of predicted); forced expiratory volume in 1 second ( $FEV_1$ ), 1.10 L (41% of predicted); maximal mid-expiratory flow, 0.81 L/min (26% of predicted); and  $FEV_1$  after administration of albuterol, 0.87 L (32% of predicted). The patient's flow volume loops showed a flattened inspiratory phase, consistent with fixed extrathoracic airway obstruction (Figure 1). A chest computed tomography scan showed severe reduction of the lumen of the upper thoracic trachea (Figures 2a and 2b). White blood cell counts revealed 10 000 leukocytes, 2% eosinophils. The blood glucose

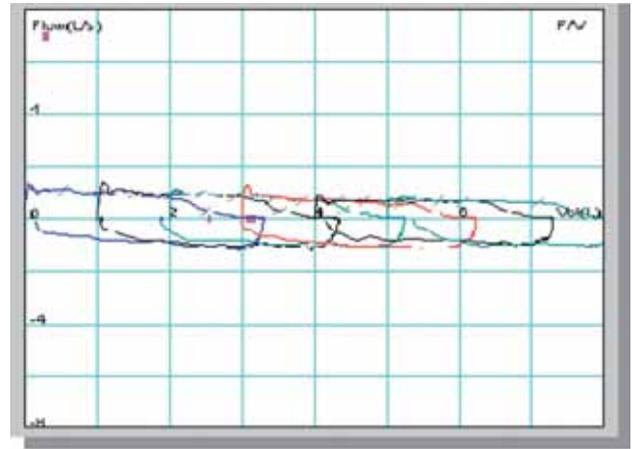


Figure 1. Flow–volume loops of a 35-year-old woman with asthma and myasthenia gravis.

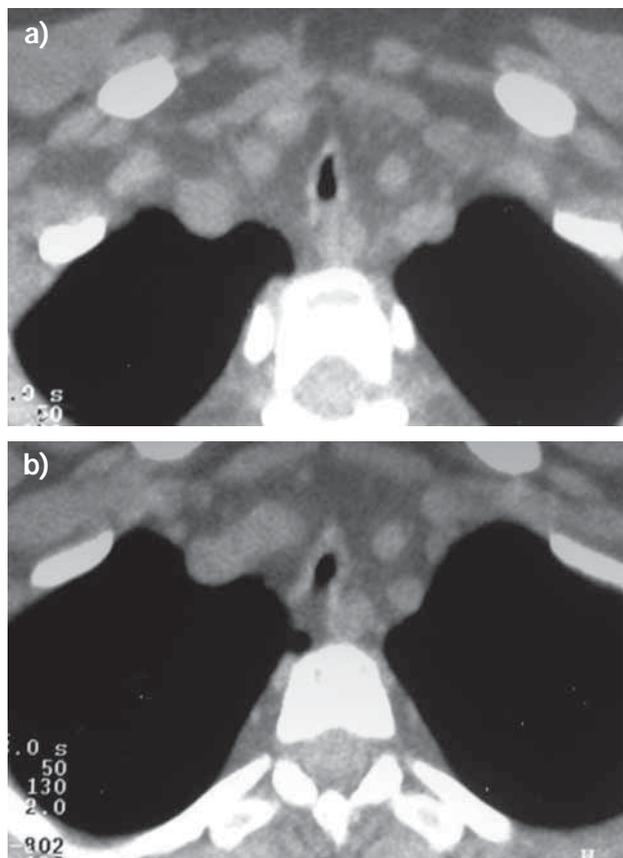
level was normal. She required treatment with an inhaled corticosteroid (budesonide, 400  $\mu$ g twice a day) and a long-acting  $\beta_2$ -agonist (formoterol, 12  $\mu$ g twice a day).

## Discussion

In this case, near-fatal asthma was complicated by tracheal stenosis and MG 3 years later. Abnormal antibody production is recognized as the basis for many diseases, among them asthma and autoimmune diseases. It is not unusual to find 2 or more of these diseases in the same patient. However, a search of the medical literature from 1960 to 2005 located only 6 studies reporting such an association between asthma and MG [4–9]. It is noteworthy that in both diseases the respiratory muscles are mechanically disadvantaged, a situation which may result in severe dyspnea.

A longitudinal study has suggested that asthma severity may be established early in childhood and worsen with age and duration of disease [10]. Severe asthma can exacerbate and progress to near-fatal or fatal asthma. In a case–control study, near-fatal episodes were associated with prior life-threatening asthma attacks, hospital admission in the previous year, a higher rate of prior mechanical ventilation, and less use of  $\beta_2$ -agonists [11]. In the present study, the patient had had asthma since she was 5 years old and clinical manifestations, apparently, had worsened over last 30 years. Despite treatment, control of her asthma symptoms had not been achieved. However, we cannot be assured of her understanding of her asthma or her compliance with treatment before she attended our outpatient clinic.

The most common cause of laryngotracheal stenosis is trauma, which can be internal (prolonged endotracheal intubation, tracheotomy, surgery, irradiation, endotracheal burns) or external (blunt or penetrating neck trauma). In the United States of America, tracheal stenosis affects 4% to 13% of adults and occurs in 1% to 8% of neonates after prolonged intubation [12]. In the present case, prolonged intubation was



Figures 2a and 2b. Computed tomography scans of the chest of a 35-year-old woman with asthma and myasthenia gravis.

associated with stenosis and clinical manifestations of upper airway obstruction developed a few weeks after hospital discharge.

Viruses constitute common triggers of asthma exacerbation in adults and viral infections have also been postulated as initiators of most autoimmune diseases through tissue damage, exposure to self-antigen and molecular mimicry. Our patient's asthma exacerbation was provoked by an airway viral infection, which may have activated her latent autoimmune disease.

MG is an uncommon autoimmune disease characterized by a fluctuating, abnormal weakness with remissions and exacerbations involving 1 or several skeletal muscle groups, mainly caused by antibodies to the acetylcholine receptor at the post synaptic site of the neuromuscular junction. The disease has 2 peaks: one between 20 and 40 years of age, mainly in women, and the other between 60 and 80 years of age shared equally by men and women [1]. The diagnosis of MG is based on history and typical clinical symptoms. Ocular symptoms such as diplopia and ptosis occur early in the majority of patients. The early onset form includes AChR antibody positivity and is a non-thymoma-related, generalized MG, affecting axial muscles, loss of facial expression, speech difficulties, and chewing and swallowing problems. Serum acetylcholine receptor antibodies (35%-50% in ocular MG),

abnormal results on repetitive nerve stimulation, single-fiber electromyography, or abnormal curare sensitivity are not predictive of those who are more likely to develop generalized MG [1].

Vocal cord dysfunction syndrome presents with sudden onset and offset of wheezes and stridor in an anxious young person with a cough, upper respiratory tract infection, or hoarseness and is usually misdiagnosed as bronchial asthma, according to Puttman and Wise [13]. This condition may present with or without asthma and is caused by paradoxical adduction of the vocal cords in inspiration; it often persists during expiration and disappears with panting, according to the same authors, who also observed upper airway obstruction of up to 80% in patients with MG. They concluded that such obstruction in these patients is much more common than is usually reported. Thus, we cannot reject the hypothesis that even before our patient's first life-threatening asthma attack she might have had asthma-related vocal cord dysfunction.

Spirometry with recording of flow-volume loops is important in the diagnosis of upper airway disease in any case. Extrathoracic fixed obstruction changes were observed in the inspiratory and expiratory limbs of our patient's flow-volume loops. These changes can be attributed to tracheal stenosis that masks partially variable asthma airflow obstruction. Interestingly, her lung function declined overall during maneuvers after administration of the bronchodilator (data not shown), an event which could suggest some respiratory muscle weakness. However, she performed each and every spirometry maneuver without symptoms or complaint in both phases (before and after bronchodilator application). The weakness and fatigability of voluntary muscles in MG characteristically exacerbate with exercise and improves with rest. Symptoms are also provoked or worsened by exposure to temperature extremes, infections, menses, and excitement. The typical spirometric pattern in patients with respiratory muscle weakness is a restrictive ventilatory defect with fairly well preserved forced expiratory flows.

In conclusion, the association of asthma and MG is uncommon and few studies have discussed it in the last 45 years. Iatrogenic stenosis of the trachea is a quite prevalent event that aggravated her severe obstructive condition. Severe asthma related to a previous near-fatal asthma episode and concomitant MG enormously increase the risk of other life-threatening crises.

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