

Asthma as a Cause of Persistent Dyspnea in Treated Myasthenia Gravis Patients

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Key Words

Asthma · Myasthenia gravis · Pulmonary function tests · Pyridostigmine

Abstract

Aims: The aim of this study was to evaluate the proportion of patients with treated myasthenia gravis (MG) who present with dyspnea not related to MG. **Methods:** We analyzed the files of 63 consecutive adult patients with treated MG and persistent dyspnea who had been referred to our Pulmonary Function Test (PFT) Department between 2000 and 2010. **Results:** We observed that asthma was the first cause of MG-unrelated dyspnea in MG patients, with 9 patients (14%) presenting with asthma-related PFT abnormalities. Six patients had asthma for several years before developing MG, and 3 patients (4%) developed asthma a few months after MG was diagnosed, suggesting a non-coincidental association between the two conditions. In all 3 cases, asthma appeared in elderly patients with severe late-onset AchR-Ab- positive MG, treated with pyridostigmine and corticosteroids and/or intravenous immunoglobulins. In all 3 patients, β_2 -adrenergic agonist treatment allowed only partial control of dyspnea. In one case, respiratory symptoms were alleviated when pyridostigmine dosage was reduced. **Conclusions:** Patients with treated MG and persistent dyspnea should be investigated for asthma using PFT before being diagnosed

with refractory MG. If asthma is diagnosed, a bronchodilator treatment should be instituted and a reduction in pyridostigmine dosage should be proposed.

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Introduction

Myasthenia gravis (MG), an autoimmune disorder affecting the neuromuscular junction, frequently provokes dyspnea as a result of respiratory muscle weakness. Persistent dyspnea in patients with treated MG may lead to the diagnosis of refractory MG, with subsequent aggressive immunosuppressive treatment [1]. Interestingly, a few reports have demonstrated that dyspnea in MG may sometimes be the result of asthma and not of muscle weakness, with important consequences for the management and treatment of patients. However, the proportion of MG patients with asthma-related persistent dyspnea has scarcely been addressed until now.

In this context, we reviewed the pulmonary function tests (PFT) of patients with treated MG and persistent respiratory symptoms, in search of MG patients with dyspnea not related to MG.

A.E.-L. and C.P. contributed equally to this work.

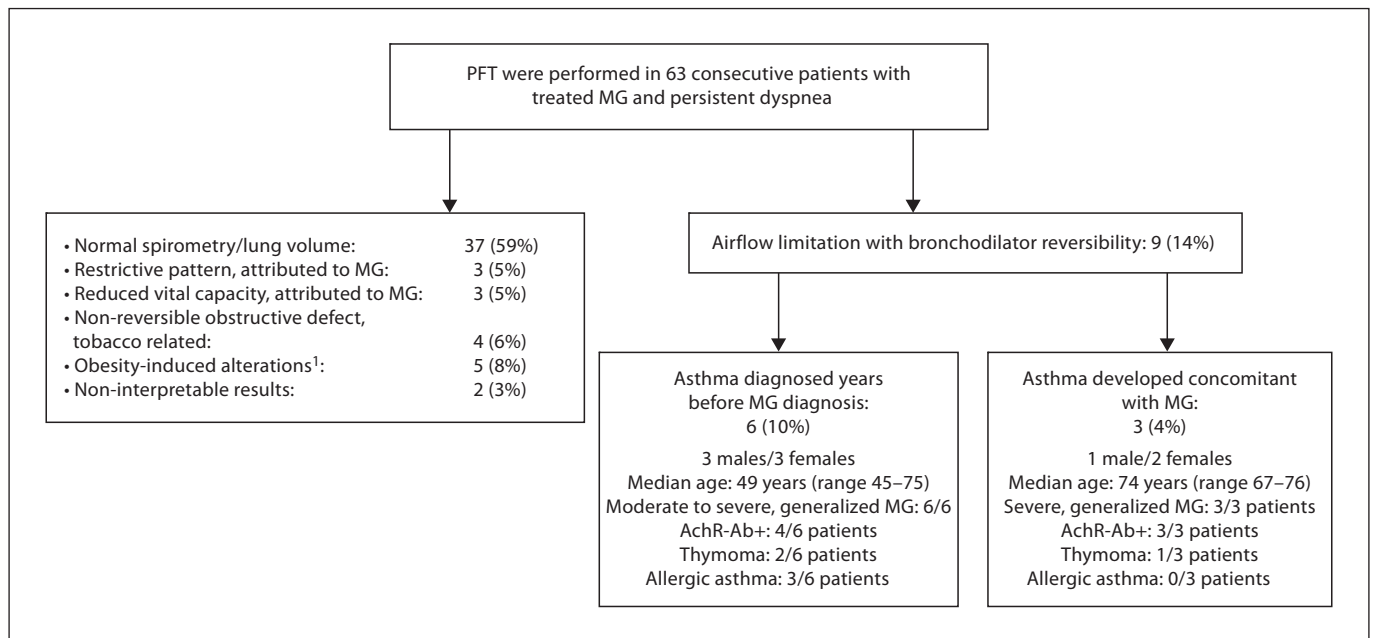


Fig. 1. Results of PFT performed in 63 patients with treated MG and persistent dyspnea. ¹ Reduced functional residual capacity and reserve expiratory volume, and body mass index >30.

Patients and Methods

We retrospectively analyzed the files of all consecutive adult patients (age >18 years) with treated MG who had been referred to the PFT Department at the University Hospital of Strasbourg, France, between 2000 and 2010, for persistent dyspnea. The diagnostic procedures were conducted according to the local ethics committee, and asthma was diagnosed by a pulmonologist following the established diagnostic criteria [2]. All patients underwent standardized clinical examinations and PFT. Lung volume measurements, flow-volume curves and reversibility tests were performed using an MS-PFT device (Jaeger USA Masterscreen Diffusion, VIASYS Healthcare, Yorba Linda, Calif., USA), following the American Thoracic Society/European Respiratory Society 2005 recommendations.

Results

PFT were performed because of persistent dyspnea in 63 treated MG patients (fig. 1). Thirty-seven patients had spirometry values in the range of normal, 3 had a restrictive pattern attributed to MG, 3 had an isolated reduced vital capacity attributed to MG, 4 had a tobacco-related non-reversible obstructive ventilatory defect, 5 had obesity-induced lung volume alterations, and the PFT of 2 patients did not meet acceptability criteria. Nine never-

smokers, representing 14% of all cases, had airway obstruction with a positive response to β_2 -adrenergic agonist challenge test. Six of these patients had been diagnosed with asthma several years before being diagnosed with MG. The 3 remaining patients, free of history of lung disease, allergy and smoking, developed asthma 3–6 months after MG was diagnosed. Their clinical characteristics are detailed in table 1. Their MG treatment included pyridostigmine. According to the Global Initiative for Asthma criteria, all 3 patients undoubtedly had asthma, i.e. 'recurrent episodes of wheezing, breathlessness, chest tightness and coughing usually associated with widespread, but variable airflow obstruction within the lung that is often reversible either spontaneously or with treatment' [2]. They were not obese (body mass index from 25 to 28) and they had no history of gastroesophageal reflux, heart failure and β -blocker treatment. Asthma symptoms were partially controlled with β_2 -adrenergic agonists and inhaled corticosteroid treatment. Interestingly, PFT were performed in 1 of these 3 patients at the very beginning of the disease and were normal. Six months after thymectomy, while treated with pyridostigmine and oral corticosteroids, this patient developed episodes of acute dyspnea, and PFT showed airflow limitation, partially controlled with bronchodilators. Later,

Table 1. General characteristics, treatment and outcome of 3 patients with MG who developed asthma

Pa-tient	Age years/ sex	MG type	MG treatment when asthma developed	Interval between first signs of MG and first signs of asthma, months	PFT at the time of asthma diagnosis	Asthma outcome
1	76/F	AchR-Ab positive	corticosteroids IVIG pyridostigmine	3	FEV ₁ /VC: 60% baseline FEV ₁ : 1.2 liters (66%) PB FEV ₁ : 1.4 liters (+14%)	partial control with salmeterol and salbutamol
2	67/F	AchR-Ab positive type I thymoma	corticosteroids pyridostigmine	6	FEV ₁ /VC: 58% baseline FEV ₁ : 1.1 liters (59%) PB FEV ₁ : 1.3 liters (+17%)	partial control with budesonide, formoterol, and reduced pyridostigmine dosage
3	74/M	AchR-Ab positive	IVIG pyridostigmine	4	FEV ₁ /VC: 62% baseline FEV ₁ : 2.8 liters (91%) PB FEV ₁ : 3.2 liters (+13%)	partial control with salmeterol and salbutamol

The FEV₁/VC ratio was decreased in all patients, reflecting airway limitation. The increase in FEV₁ obtained after inhalation of a bronchodilator (PB FEV₁) was significant in all patients. IVIG = Intravenous immunoglobulin; FEV₁ = forced expiratory volume in 1 s, expressed as absolute value and percentage of predicted; VC = slow vital capacity; PB FEV₁ = post-bronchodilator FEV₁, expressed as absolute value and bronchodilator-induced increase (percentage of the baseline FEV₁ value).

contemporary to the reduction in corticosteroids and pyridostigmine dosage, respiratory symptoms were progressively alleviated and PFT significantly improved.

Discussion

A major aim of spirometry and lung volume measurements in MG patients is to identify non-MG-induced lung disorders that may account for the patient's respiratory symptoms. Indeed, in our series as well as in the literature [3], most MG patients presented with PFT values in the range of normal, and MG-induced restrictive ventilatory patterns or low vital capacity were rarely observed. Surprisingly, in our study, we found that the first cause of dyspnea not related to MG was asthma (14% of our 63 patients), followed by obesity and tobacco-induced PFT abnormalities, while in the general adult population, tobacco-induced chronic obstructive pulmonary disease prevalence (10%) and obesity prevalence (16%) are higher than asthma prevalence (6%) [2]. This result suggests that the coexistence of MG and asthma may not be coincidental.

Several patients with asthma and MG have already been reported in the literature [4–6] with no obvious pattern. Indeed, this association has been described in patients of various ages, with or without allergic status, and with asthma developing before or after MG at different time intervals. Such heterogeneity may suggest a coincidental association between the two affections. In con-

trast, the 3 patients reported here have striking similarities that suggest a non-coincidental association between the two conditions: in all these cases, asthma appeared in elderly patients with no smoking or allergy history, and severe late-onset antibodies to the skeletal muscle acetylcholine receptor (AchR-Ab)-positive MG, treated with pyridostigmine and corticosteroids and/or intravenous immunoglobulin. Also, asthma appeared in all cases a few months after MG was diagnosed and was partially controlled by β_2 -adrenergic agonist treatment. In keeping with the concept of a pathophysiological link between MG and asthma, it has been observed in one study that half the patients with intrinsic asthma presented with MG-like electrophysiologic abnormalities, i.e. a significant decrement on repetitive nerve stimulation [7].

One may hypothesize that asthma is an immune disease associated with MG. In line with this concept, antibodies directed against β_2 -adrenergic receptors have been reported in MG patients [8]. However, whether these antibodies may impair the ability of epinephrine to bind to β_2 -adrenergic receptors and facilitate bronchospasm remains unclear. Moreover, abnormalities in cardiac autonomic control [9] and ganglionic AchR-Ab [10] have been reported in subsets of patients with MG, suggesting there may be an imbalance between sympathetic and parasympathetic neural regulation in some patients with MG. Such an imbalance may facilitate a chronic increase in airway smooth muscle tone. Lastly, asthma and MG may share immune system abnormalities such as altered func-

tion of T-natural regulatory cells. T-regulatory cells play a central role in the control of the lymphocyte-driven airway inflammation observed in asthma [11]. Overall, one cannot exclude that asthma developed as an immune disorder associated with MG in the cases reported here.

It could also be hypothesized that asthma was the result of pyridostigmine treatment. Indeed, pyridostigmine inactivates acetylcholinesterase in synapses, leading to an increased amount of Ach available to bind to nicotinic and bronchial muscarinic AchR. Consequently, pyridostigmine may induce airway smooth muscle contraction by increasing bronchial muscarinic AchR activity. Pyridostigmine has no significant effect on bronchial hyperresponsiveness in normal subjects and asthmatic patients [12] but it provokes a reduction in the forced expiratory volume in 1 s/forced vital capacity ratio, which reflects airflow limitation, in MG patients [4]. Furthermore, pyridostigmine given to MG patients with airflow limitation leads to further increases in airway resistance that can be partially reversed by ipratropium bromide [13]. In our patients, asthma developed in all cases a few weeks after pyridostigmine treatment was introduced and, in 1 case, asthma symptoms were alleviated when pyridostigmine dosage was reduced. Therefore, it cannot be excluded that asthma was at least in part provoked by pyridostigmine therapy in the 3 cases described here.

Considering all the above-mentioned data, a direct connection between asthma and MG is difficult to demonstrate and it remains unclear whether the association of both conditions is coincidental or not. As both asthma and MG are immune diseases, they may have common pathophysiological mechanisms or at least common pre-

disposing factors. Pyridostigmine, by increasing airway resistance, may also contribute to asthma symptoms developing in MG patients.

The interpretation of our data is limited by the retrospective and hospital-based design. As a consequence, our patients may not be representative of typical MG populations, and larger studies are needed to accurately establish the prevalence of asthma in MG patients. Nevertheless, since only limited clinical data are available on asthma in MG patients, we believe our results remain of direct relevance to clinical practice.

Our report demonstrates that dyspnea in MG patients is asthma related and not related to myasthenic muscle weakness in a significant subset of patients. This is of major clinical importance as MG patients with persistent dyspnea may be diagnosed with refractory MG and treated with aggressive immunosuppressive therapies, when in fact they may rather need asthma treatment and reduced pyridostigmine dosage. In our view, all patients with MG and dyspnea should be investigated for asthma using PFT and a β_2 -adrenergic agonist challenge test if an obstructive pattern is observed. If asthma is diagnosed, bronchodilators should be instituted and a reduction in pyridostigmine dosage should be proposed.

Disclosure Statement

Dr. de Sèze serves on scientific advisory boards for and has received honoraria from Biogen Idec, LFB, Merck Serono, Sanofi-Aventis, and Bayer Schering Pharma, and serves on the editorial board of *Revue Neurologique* (Paris).

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