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ORIGINAL ARTICLE

Prevalence of over-/misdiagnosis of asthma in patients referred to an allergy clinic

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Abstract

Objective: Increasing asthma incidence may be due to an overall increase in asthma awareness by physicians, potentially resulting in overdiagnosis. One of the unique features of asthma is bronchial hyperresponsiveness, which can be assessed by methacholine bronchial challenge (MBC). Overdiagnosis may result in over- or mistreatment. The aims of this study were to describe the prevalence of the over-/misdiagnosis of asthma and the use of anti-asthmatic drugs in patients with asthma-like symptoms who had not yet undergone a respiratory function assessment to confirm the diagnosis of asthma. **Methods:** This was a retrospective study analyzing all MBCs performed by our Outpatient Allergy Clinic in a two-year period to confirm/exclude the diagnosis of asthma in patients referred by general practitioners and complaining of asthma-like symptoms. Anti-asthmatic medications used by the patients until the MBC date were recorded. **Results:** 43.8% of the reviewed MBCs were positive and 37.4% of the patients with a positive MBC were previously taking anti-asthmatic drugs (568.8 ± 76.4 mcg mean beclomethasone equivalents), compared to 51.2% of those patients with a negative MBC (464.8 ± 57.8 mcg). No differences were found in the daily doses of inhaled corticosteroids or other anti-asthmatic drugs, or in the duration of treatment before the assessment of bronchial hyperresponsiveness. **Conclusions:** A sizeable percentage of subjects who reported physician-diagnosed asthma had a negative MBC. Nevertheless, a greater proportion of negative MBC patients were taking anti-asthmatic drugs compared to those with a confirmed diagnosis of asthma, illustrating that the overdiagnosis of asthma may lead to over- and mistreatment of respiratory symptoms.

Keywords

Asthma, lung function, methacholine, misdiagnosis, overdiagnosis

History

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Introduction

In the past, the underdiagnosis of asthma by primary care physicians was reported to be an important problem [1–4]. However, the intense focus on asthma as a prevalent and treatable condition over the past decade may have resulted in a heightened awareness among physicians and led to asthma being more frequently diagnosed.

Unfortunately, an increase in the index of suspicion for asthma in adults with respiratory complaints may also have led to the mislabeling of non-asthmatic subjects as asthmatics. There has been some attention in the popular media on the overdiagnosis of asthma, and some studies have mentioned this emerging clinical problem [5–8].

Inappropriate diagnosis of asthma is most likely to occur when physicians rely on clinical evaluation alone rather than objective testing. Asthma is defined as an inflammatory disorder of the airways characterized by: (i) paroxysmal or

persistent symptoms (dyspnea, chest tightness, wheeze and cough) with (ii) variable airflow limitation and (iii) airway hyperresponsiveness to a variety of stimuli [9]. Presumably, individuals not meeting these criteria may not suffer from the disease.

One of the unique features of asthma, airway hyperresponsiveness, can be easily assessed with a methacholine bronchial challenge (MBC), which consists of inhaling increasing doses of methacholine and measuring lung function after each inhalation. The concentration of medication required to decrease FEV₁ by 20% is noted (PC₂₀FEV₁) and considered to be diagnostic. Unfortunately, MCB is time consuming and may be uncomfortable for patients. As a result, this fundamental test is often underutilized in clinical practice.

The aims of this study were:

- (1) to analyze the prevalence of positive MBCs in patients complaining of asthma-like symptoms, with normal spirometry, who were referred to an allergy clinic and
- (2) to describe the use of anti-asthmatic drugs in patients with respiratory symptoms before a formal diagnosis of asthma by MBC, according to the drug prescription file of the general practitioner (GP) of each enrolled patient.

Methods

Study design

This was a retrospective study analyzing all MBCs performed by our Allergy Outpatient Clinic from 1 January 2010 until 31 December 2012. All MBCs were performed to confirm the diagnosis of asthma in patients referred by GPs and complaining of asthma-like symptoms, but with normal spirometry.

All MBCs were performed according to international recommendations [10] and there was a minimum 7-day washout period before the test.

Patients

According to our clinic database, approximately 100 patients/year, referred by GP for suspected asthma, have been found to have normal spirometry and were further tested using a MBC. We reasoned that a two-year period appeared to be appropriate to investigate how often the diagnosis of asthma could be confirmed in these patients, taking into account that the prevalence of misdiagnosis of had been previously reported to be near 30% [8].

A total of 226 patients (130 females, 57.5%; mean age 37.4 ± 1.3 years, range: 15–70 years) who underwent the MBC for asthma diagnosis have been included in the study. All patients had been referred to the clinic for suspected asthma by their GP. All patients who had asthma-like symptoms and normal spirometry were included in the study and the MBC result (positive or negative, according to international guidelines) [9] was recorded.

Patients' clinical records (including BMI) up to the date of MBC were reviewed, and information regarding the patients use of anti-asthmatic drugs was noted (type of treatment, dosage, duration of treatment before MBC). The source of the drug prescriptions data was the drug prescription file of the GP of each enrolled patient. In Italy, all district inhabitants must choose their GP and almost all GP drug prescriptions are saved in electronic files. The doses of the different inhaled corticosteroids were converted to beclomethasone equivalents.

Evaluation of the direct cost of treatment

The pro-capita cost of treatment before the MBC assessment was computed using the defined daily dose (DDD) index and multiplied by the duration of treatment (number of days). The DDD index is a statistical measure of drug consumption defined by the World Health Organization to standardize the comparison of drug usage between different drugs [11].

It should be emphasized that the DDD is a unit of measurement and does not necessarily reflect the recommended or prescribed daily dose. The DDD provides a fixed unit of measurement, independent of price and dosage form (e.g. tablet strength), enabling the researcher to assess trends in drug consumption and to perform comparisons between population groups.

Statistics

The sample size was determined by considering a 30% estimated prevalence of misdiagnosis of asthma when the diagnosis is not supported by respiratory function tests [8].

The clinic database identified that approximately 100 patients per year were referred by a GP for suspected asthma, and on exhibiting normal spirometry, were evaluated using a MBC. A two-year period was therefore considered an appropriate duration for obtaining sufficient patient numbers.

A descriptive analysis of all known variables concerning all included patients was performed. Continuous variables were evaluated with the normality test of Kolmogorov–Smirnov and compared with the ANOVA or Mann–Whitney test, depending on the normality of the distribution. Categorical variables were compared using Fisher's exact test. All data were analyzed using SPSS v. 20.0 software (SPSS, Chicago, IL).

Results

Ninety-nine of the 226 (43.8%) patients had positive MBC results, and 102 (45.1%) were using anti-asthmatic drugs before undergoing the MBC.

The demographic and drug consumption data of the patients compared by MBC results are reported in Table 1. The proportion of patients already receiving anti-asthmatic drugs was 45.1% (102/226 patients) and was significantly lower in the subgroup of patients with a positive MBC compared to those with a negative MBC (37.4% vs 51.2 %, respectively, $p = 0.038$) (Figure 1). No significant differences in body mass index, gender or age were found in the comparison of patients with positive versus negative MBC or treated asthma versus untreated patients.

The mean duration of treatment before MBC was 25.1 ± 4.4 months, and the mean daily dose of inhaled corticosteroids expressed as beclomethasone equivalents was 503.3 ± 46.1 mcg. No significant difference was found for the duration of treatment and beclomethasone equivalent dose between patients with positive and negative MBCs.

Additionally, no difference was found between the use of other anti-asthmatic drugs (i.e. long-acting beta2-agonists or leukotriene-receptor antagonists) between those patients with positive and negative MBCs.

The mean direct cost of treatment, expressed as DDD, was 722.1 ± 201.6 USD. Patients with a negative MBC had a mean DDD of 965.3 ± 333.1 USD, which was higher than the DDD of patients with a positive MBC (524.3 ± 169.7 USD, $p = 0.279$), but the difference was not statistically significant (Figure 2).

Discussion

The main result of this study is that a sizeable percentage of subjects who report physician-diagnosed asthma and have been previously treated for this disease have a negative MBC.

In patients with normal or near-normal spirometric values, assessment of airway responsiveness is safe and significantly better than other tests in discriminating patients with asthma from patients with conditions commonly confused with asthma. The test is sensitive so normal results provide the strongest evidence against a diagnosis of asthma [12].

Yurdakul et al. [13] describe a much higher sensitivity for MBC compared with FEV1 reversibility and PEFV variability for asthma diagnosis among patients attending an outpatient asthma clinic. Furthermore, Aaron et al. [8] suggest that

Table 1. Demographic and drug consumption data of patients, compared according to the MBC result.

	All patients (n = 226)	MBC positive patients (n = 99)	MBC negative patients (n = 127)	p Value (positive vs negative MBC patients)
Mean age	37.4 ± 1.3 years	37.0 ± 0.22 years	37.6 ± 1.6 years	0.622
Gender ratio (M/F)	0.74	0.68	0.79	0.578
Proportion of already treated patients	102/226 (45.1%)	37/99 (37.4%)	65/127 (51.2%)	0.038
Mean duration of treatment	25.1 ± 4.4 months	25.3 ± 7.6 months	24.9 ± 5.4 months	0.649
Mean daily beclomethasone equivalents	503.3 ± 46.1 mcg	568.8 ± 76.4 mcg	464.8 ± 57.8 mcg	0.335
DDD × days of treatment	772.1 ± 201.6 USD	524.3 ± 169.7 USD	965.3 ± 333.1 USD	0.279

Bold value represents statistical significance.

Figure 1. Proportion of patients with positive or negative MBC, and distribution of already treated patients in the two group of patients ("Treated" vs "Naive").

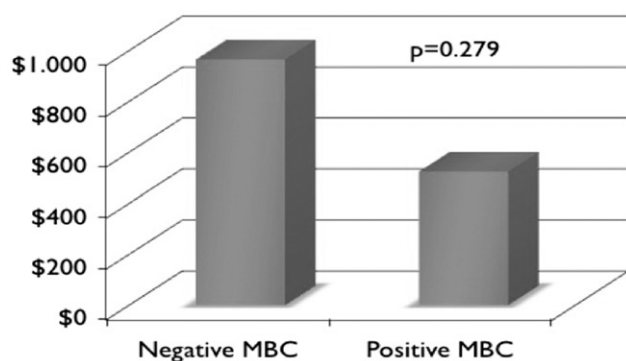
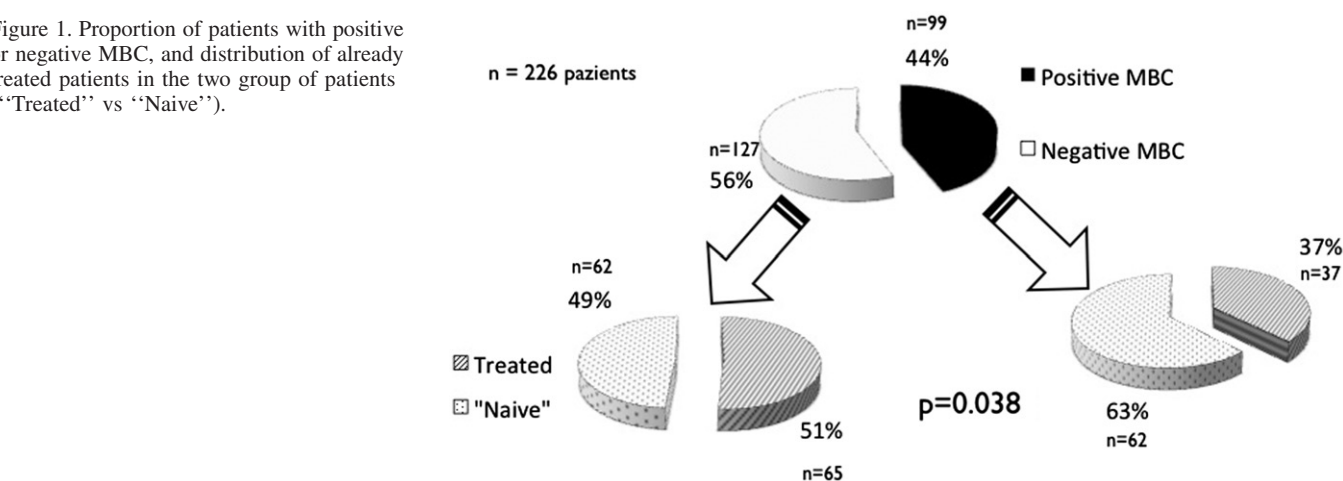


Figure 2. DDD for anti-asthmatic drugs multiplied for the duration of treatment in patients with positive or negative MBC.

asthma diagnosis could be confirmed in only 16% of patients by means of post-bronchodilator spirometry at the time of testing and in 72% of patients by means of bronchial challenge testing with methacholine. Finally, Luks et al. [7] suggest that only 10.8% of patients were diagnosed with asthma using simple pre- and post-bronchodilator spirometry at the time of testing, while MBC resulted in a confirmation rate of 61.7% and an exclusion rate of 27.3% among individuals whose lung function was reported to be in the normal range at clinical presentation. Interestingly, a greater proportion of patients with a negative MBC were taking anti-asthmatic medications compared to those patients with a confirmed diagnosis of asthma.

Taken together, these data reveal that there is consistently over-/misdiagnosed asthma, which may lead to over- and mistreatment of respiratory symptoms.

Many other conditions can cause symptoms similar to those of asthma. The differential diagnosis of asthma includes chronic obstructive pulmonary disease (COPD), chronic bronchitis or emphysema, congestive heart failure, extra-thoracic airway hyperresponsiveness syndromes (e.g. vocal cord dysfunction, VCD), gastroesophageal reflux disease, mechanical obstruction of the airways, tumor/neoplasm and cough associated with upper airway disease (rhinitis and rhinosinusitis). Infrequent causes of wheezing include pulmonary embolism, pulmonary infiltrates with eosinophilia and some medications (e.g. angiotensin-converting enzyme inhibitors) [12]. Several of the above conditions may be strongly suspected upon conducting a spirometric evaluation (another underutilized tool in patients with respiratory symptoms); for instance, COPD may be suspected by the detection of a non-reversible bronchial obstruction, or extrathoracic airway limitations may lead to suspicion of VCD or other extrathoracic hyperresponsive syndromes.

The long duration of treatment with anti-asthmatic agents (which was not significantly different in patients with confirmed asthma compared to those with a negative MBC) before performing MBC to confirm or exclude the diagnosis of asthma confirms the underutilization of lung function tests in respiratory disorders, despite the recommendations of international guidelines that the diagnosis of asthma requires the assessment of airway obstruction and its reversibility or the assessment of airway hyperreactivity [9].

The direct cost of over- or mistreatment of respiratory symptoms seems to be substantial. It is also interesting to note that, in this study, the total cost of anti-asthmatic treatment was higher in patients who were found to be non-asthmatic; however, this was not significant.

The main limitation of this study is that it is retrospective and not prospective, therefore providing limited information on the final diagnosis of patients complaining asthma-like symptoms without the evidence of airway hyperresponsiveness as these patients were lost at follow-up and referred to other specialists (i.e. ENT, gastroenterologists, pneumologists, etc.) to make the final diagnosis and giving correct treatment.

Conclusion

This study suggests that a clinical diagnosis not supported by the lung function tests recommended by international guidelines may lead to the over-/misdiagnosis and over-/mistreatment of asthma. Improving the systematic support and education of GPs in diagnostic testing and decision-making may diminish the prescription and overtreatment of inhaled corticosteroids, thus reducing expensive and needless treatment of non-asthmatic patients.

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Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper. This study has been conducted without any external fund.

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