Prior Diagnosis and Treatment of Patients With Normal Results of Methacholine Challenge and Unexplained Respiratory Symptoms*

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Objective: Previous research indicates that asthma has been underdiagnosed. However, we suspect that recent widespread attention to the underdiagnosis of asthma has led to an overdiagnosis of asthma in some settings. We therefore sought to examine prior diagnosis and treatment of patients referred to our facility and subsequently found to have no objective evidence of variable airflow limitation.

Design: Retrospective chart review.

Setting: Hospital-based asthma center.

Patients: A referred sample of 263 patients in whom a methacholine challenge (MCC) was conducted after evaluation by our pulmonologists; complete medical histories were available.

Main outcome measures: Prior respiratory diagnoses, duration of treatment with asthma medications, and diagnosis following assessment by our pulmonologists in 175 patients with a provocative concentration of the substance causing a 20% fall in FEV₁ (PC_{20}) greater than 8.0 mg/mL and 88 with a PC_{20} of 8.0 mg/mL or less.

Results: Of those with a PC_{20} greater than 8 mg/mL, a diagnosis of asthma or possible asthma prior to the challenge study was recorded by their primary care physician in 129 patients (74%). One hundred sixty of 172 patients (88%) with a PC_{20} greater than 8 mg/mL were diagnosed as not having asthma by our pulmonologists; 109 of 172 patients (62%) had been previously treated with asthma medication(s). The mean duration of asthma treatment was 25.9±56.3 months, and there was no significant difference in the duration of treatment between this group and those who had a PC_{20} of 8 mg/mL or less. Most of those treated received inhaled β₂-agonists and inhaled corticosteroids. Approximately 61% received two or more classes of medications.

Conclusions: The misdiagnosis of asthma occurs commonly in the referral practice of a tertiary care asthma center. The more frequent use of objective pulmonary function testing in primary practice might reduce the problem of delayed diagnosis and inappropriate therapy for respiratory symptoms.

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Key words: asthma; diagnosis; methacholine challenge

The underdiagnosis of asthma has been identified as a significant factor contributing to reported increases in asthma morbidity and mortality.1-3 Thus, continuing medical education has focused on raising clinical suspicion of asthma when various respiratory symptoms occur.3-6 Health-care professionals are, in effect, encouraged to diagnose asthma. We suspect that a byproduct of such efforts has been an incorrect diagnosis of asthma and the inappropriate prescription of asthma therapy in many individuals.

There are a variety of diseases, both pulmonary and nonpulmonary, which may lead to respiratory symptoms. Several reports have highlighted some of the more dramatic and infrequent disorders that may mimic symptomatic asthma, with little data available to help estimate the magnitude of the problem.7-9

We therefore sought to determine if there is a population of nonasthmatics who have been diagnosed and treated for asthma. Specifically, we have examined the prior diagnosis and treatment of patients referred to our facility who were subsequently shown to have no evidence of airway hyperresponsiveness by methacholine challenge.

MATERIALS AND METHODS

Study Design

We conducted a retrospective review of hospital pulmonary function laboratory data on 500 patients referred to The Toronto Hospital for a methacholine challenge between November 1987 and August 1993. When patients had also been seen in consultation by a pulmonologist at the center prior to the methacholine challenge, medical histories were studied in detail using available chart data. Patients were divided into two groups: those without an airway response (AR) after inhaling methacholine at 8.0 mg/mL (provocative concentration causing a 20% fall in FEV₁ [PC_{20}] >8.0 mg/mL) and those with an AR, according to the following criteria: FEV₁/FVC <70%, FEV₁ <61% of predicted, or a fall of 20% or greater in FEV₁.

The AR was considered to be positive if the mean change in FEV₁ 20 minutes after the last dose of methacholine was greater than or equal to 20% of the baseline FEV₁ or if the postchallenge FEV₁ was less than 61% of predicted.

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mg/mL) and those with airway hyperresponsiveness (PC$_{20}$ ≤8.0 mg/mL). We collected medical history information primarily from the consultation letters prepared by the respiratory consultant and from a patient questionnaire administered routinely to all new patients. When data were unavailable or incomplete from these sources, letters of referral, pulmonary function testing requisition forms, and direct patient contact were used.

**Treatment With Asthma Medications**

The duration of treatment with asthma medications was estimated as the duration of treatment with the class of medication given for the longest period of time. When two medications in the same class (eg, beclomethasone and budesonide) were used by one individual, the duration of treatment with that medication class was calculated as the sum of the duration of the treatment with each of the medications.

**Alternate Diagnoses**

We collected from consultation notes the alternate diagnoses given to patients by four asthma center respiratory physicians following methacholine challenges and clinical assessment. The diagnosis was said to be "possible" when a physician remarked that he or she was uncertain of the alternate diagnosis, or for those in whom a tentative diagnosis was made but not confirmed due to lack of follow-up.

**Methacholine Challenge**

Methacholine inhalation challenge tests were performed according to the method described by Hargrave and coworkers.\textsuperscript{10} Medications withheld prior to the test were as follows: (1) beta-blockers, 48 h; (2) inhaled bronchodilators, 6 to 8 h; (3) salmeterol, 24 h; (4) theophyllines, 24 h; and (5) sustained-release theophylline preparations, 48 h. Inhaled and oral steroid therapy was not routinely withheld. The level of bronchial hyperreactivity was expressed as the PC$_{20}$. Testing was conducted using increasing concentrations of methacholine up to 16 mg/mL or until FEV$_1$ decreased by 20% or more from the baseline value. A PC$_{20}$ of 8 mg/mL or less was considered to represent a positive test of airway hyperresponsiveness.

**Statistical Analysis**

Results are expressed as absolute number and as means±SD for duration of treatment. Two-tailed, unpaired $t$ tests were used to compare the durations of treatment between groups (PC$_{20}$ ≤8 mg/mL and PC$_{20}$ >8 mg/mL). $\chi^2$ analysis was used to compare differences in number of classes of medications between the study groups. Results were considered significant at a $p$ value less than 0.05.

**Results**

Of the 500 patients who underwent methacholine challenge testing, 263 were referred to and assessed by physicians at the Asthma Centre of the Toronto Hospital prior to the methacholine challenge and had complete patient files available. Of these, 175 did not have an AR after inhaling 8 mg/mL of methacholine (no AR group) and 88 had an airway response after inhaling 8 mg/mL or less of methacholine (AR group). The remaining 237 patients could not be included in the analysis for the following reasons: (1) the patients were referred for a methacholine challenge by a primary care physician and not seen in follow-up by an asthma center physician; (2) patient charts could not be located; (3) patient charts were largely incomplete; or (4) patients could not be contacted by telephone.

**Demographics and Diagnosis at Referral**

The characteristics of no AR and AR groups are shown in Table 1. The mean age of patients was 40±15

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**Table 1—Characteristics of 175 Subjects With No AR to Methacholine at 8 mg/mL (No AR) and 88 Subjects With an AR to Methacholine at 8 mg/mL or Less (AR)**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No AR</th>
<th>AR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td>40±15</td>
<td>36±14</td>
</tr>
<tr>
<td>Sex, No. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>71 (41)</td>
<td>23 (26)</td>
</tr>
<tr>
<td>Women</td>
<td>104 (59)</td>
<td>65 (74)</td>
</tr>
<tr>
<td>Diagnosis at referral, No. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asthma/ possible asthma</td>
<td>129 (74)</td>
<td>77 (88)</td>
</tr>
<tr>
<td>Bronchitis/COPD</td>
<td>20 (11)</td>
<td>6 (7)</td>
</tr>
<tr>
<td>Symptom not yet diagnosed*</td>
<td>15 (9)</td>
<td>6 (7)</td>
</tr>
<tr>
<td>Other*</td>
<td>11 (6)</td>
<td>3 (3)</td>
</tr>
</tbody>
</table>

*The no AR group consisted of cough (12), and dyspnea (3). The AR group consisted of wheeze (1) and cough (5).

\textsuperscript{1}For the no AR group, other diagnoses included pneumonitis (1), fibrositis (1), pulmonary fibrosis (1), rhinitis (1), pneumonia (1), bronchiectasis (1), occupational lung disease (1), and possible sleep apnea (4). The AR group consisted of sleep apnea (3).

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**Table 2—Classes of Drugs Prescribed and Comparison of Duration of Use for Each Group**

<table>
<thead>
<tr>
<th>Medication</th>
<th>No AR (n=175)</th>
<th>AR (n=88)</th>
<th>No. (%)</th>
<th>Duration, mo*</th>
<th>No. (%)</th>
<th>Duration, mo</th>
<th>p Value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>All treatments</td>
<td>109 (62)</td>
<td>79 (90)</td>
<td>26±56</td>
<td>43±64</td>
<td>0.08</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inhaled $\beta_2$-agonists</td>
<td>89 (51)</td>
<td>72 (82)</td>
<td>29±57</td>
<td>46±66</td>
<td>0.11</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inhaled corticosteroids</td>
<td>66 (38)</td>
<td>49 (56)</td>
<td>22±37</td>
<td>15±25</td>
<td>0.33</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oral corticosteroids</td>
<td>18 (10)</td>
<td>24 (27)</td>
<td>3±7</td>
<td>—</td>
<td>—</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oral bronchodilators</td>
<td>20 (11)</td>
<td>23 (26)</td>
<td>36±66</td>
<td>25±23</td>
<td>0.58</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inhaled nonsteroidal anti-inflammatory</td>
<td>16 (9)</td>
<td>12 (14)</td>
<td>11±12</td>
<td>13±22</td>
<td>0.68</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inhaled ipratropium bromide</td>
<td>14 (8)</td>
<td>12 (14)</td>
<td>6±10</td>
<td>20±24</td>
<td>0.11</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Methotrexate</td>
<td>0 (0)</td>
<td>1 (1)</td>
<td>—</td>
<td>2</td>
<td>—</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Mean duration of treatment is calculated for those patients who received treatment.

†$p$ values refer to the duration of each treatment class.
years (62; range, 9 to 71 years) in the no AR group and 36±14 years (67; range, 9 to 76 years) in the AR group. Most patients in each group were considered by their primary care physicians to have asthma. The proportion of asthma diagnosis was significantly higher in the AR group than in the no AR group.

**Treatment With Asthma Medications**

More patients in the AR group than in the no AR methacholine group had received a prescription for at least one antiasthma medication before referral (90% vs 62%; p<0.001). Among the patients being treated, there was no significant difference in the proportion of those treated with any specific class of asthma medication (Table 2). Most patients who were treated received inhaled β2-agonists, and more than 60% of the treated patients in each group had received inhaled corticosteroid therapy. Similarly, there was no difference between groups in the duration of antiasthma therapy or the proportion of patients receiving two or more classes of antiasthma therapy before referral (Tables 2 and 3). The average duration of therapy in those patients who were treated exceeded 2 years for both groups, with most patients receiving therapy with two or more classes of drug before referral (Tables 2 and 3). Drug therapy was not limited to inhaled regimens. Among patients in the no AR group, 18 received oral steroids for an average treatment duration of 3 months. One patient received oral steroids daily for 8 months before referral.

Although data on treating physicians were not uniformly available, at least 21% of the patients had been treated in the past by a physician other than the current referring physician.

**Alternate Diagnoses**

Following referral and investigation at our center, an alternate diagnosis was given by a specialist in respiratory medicine (Table 4). Although no specific alternate diagnosis was stated in 44 patients (25%) in the no AR group, these patients were diagnosed as not having asthma. The most common alternate diagnosis given were common respiratory illnesses, including rhinitis (21%) and upper respiratory tract infections/postviral cough (16%). A diagnosis of bronchitis, COPD, or possible COPD was proposed in a minority of patients (7%). Functional causes were implicated in 14 patients (9%), and the diagnoses included hyperventilation syndrome (7), functional vocal cord dysfunction (2), supraglottic irritation (1), and deconditioning (5). A variety of other respiratory diagnoses were given to the remaining patients, including gastroesophageal reflux cough, angiotensin-converting enzyme inhibitor cough, bronchiectasis, and extrinsic allergic alveolitis.

A diagnosis of asthma or possible asthma was given to 21 (12%) patients despite having a PC_{20} greater than 8 mg/mL. Of these patients, seven (4%) had methacholine challenges in the range of 8 to 16 mg/mL. Eighty-four patients (96%) in the AR group were regarded as having asthma or possible asthma after specialist assessment. Of the four patients not thought to have asthma as the basis of their symptoms, the alternate diagnosis was not stated in two patient files, and the remaining two were given the diagnoses of rhinitis and adductor spasm, respectively.

**Analysis Using PC_{20} Greater Than 16 mg/mL as the Cutoff**

We reanalyzed the data using 16 mg/mL as the cutoff between airway hyperresponsiveness (AR_{16}) and no airway response (no AR_{16}). Using the same analyses as for the original AR and no AR groups, we obtained similar results between the two groups. Significantly more patients in the AR_{16} had a diagnosis of asthma at referral than in the no AR_{16} group (87% vs 72%). Significantly more patients in the AR_{16} group received any asthma medication (87% vs 61%; p<0.001). Furthermore, significantly more treated patients in the AR_{16} group received inhaled cortico-

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**Table 3—Number of Classes of Asthma Medications Given Prior to Referral**

<table>
<thead>
<tr>
<th>No. of Asthma Medications</th>
<th>No AR, No. (%) (n=109)</th>
<th>AR, No. (%) (n=79)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>41 (38)</td>
<td>25 (32)</td>
</tr>
<tr>
<td>2</td>
<td>38 (35)</td>
<td>19 (24)</td>
</tr>
<tr>
<td>3</td>
<td>19 (17)</td>
<td>18 (23)</td>
</tr>
<tr>
<td>≥4</td>
<td>11 (9)</td>
<td>17 (22)</td>
</tr>
</tbody>
</table>

**Table 4—Diagnosis in 175 Subjects With No Airway Response to Methacholine at 8 mg/mL (No AR) and 160 Subjects With No Airway Response to Methacholine at 16 mg/mL (No AR_{16}) Following Assessment by Asthma Center Physician**

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>No AR, No. (%) (n=175)</th>
<th>No AR_{16}, No. (%) (n=160)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asthma/possible asthma</td>
<td>21 (12)</td>
<td>14 (9)</td>
</tr>
<tr>
<td>Rhinitis</td>
<td>37 (21)</td>
<td>37 (23)</td>
</tr>
<tr>
<td>Bronchitis/COPD</td>
<td>13 (7)</td>
<td>11 (7)</td>
</tr>
<tr>
<td>Viral respiratory tract infection/postviral cough</td>
<td>28 (16)</td>
<td>27 (17)</td>
</tr>
<tr>
<td>Functional</td>
<td>15 (9)</td>
<td>14 (9)</td>
</tr>
<tr>
<td>No diagnosis, not asthma</td>
<td>44 (25)</td>
<td>41 (26)</td>
</tr>
<tr>
<td>Other*</td>
<td>17 (10)</td>
<td>16 (10)</td>
</tr>
</tbody>
</table>

*Diagnoses included were as follows: gastroesophageal reflux-induced cough (2); angiotensin-converting enzyme inhibitor-induced cough (3); bronchiectasis/possible bronchiectasis (4); fibromyalgia (2); cough due to reactive airways (1); possible eosinophilic bronchitis (1); middle lobe syndrome (1); extrinsic allergic alveolitis (2); and chemical airway irritation (1).
steroids (54% vs 38%; p<0.05). Of those treated, there was no difference in the proportion treated with all other classes of medication. Ninety-eight patients in the no AR16 were treated with medications for a mean of 26±58 months, and there was no significant difference in the mean duration of treatment between the two groups (p=0.10). The alternate diagnoses given to the no AR group were similar to those given to the original no AR group (Table 4).

**DISCUSSION**

Our data indicate that in a large tertiary care asthma center, the false-positive diagnosis of asthma is not a rare problem and is often associated with prolonged periods of unnecessary treatment with multiple medications. Approximately 75% of our patients unresponsive to methacholine at doses of 8 mg/mL or less were previously diagnosed by a physician as having asthma. Sixty-two percent had been treated with one or more antiasthma medications for asthma for an average duration of approximately 2 years. Some nonasthmatic patients being treated with antiasthma therapy had used such medications for as long as 36 years. There was no significant difference in the duration of treatment with medications between those who had airway hyperresponsiveness compared to those with no AR to methacholine at doses of 8 mg/mL or less.

Case reports and review articles have identified diseases that may be confused with asthma, but none suggest that the overdiagnosis of asthma is a significant health-care issue.7-9,11 Our data do not allow us to estimate the true prevalence of false-positive asthma diagnoses. However, in an earlier review of patients referred to our center for asthma management, we found that 5% of presumed asthma sufferers did not suffer from the disorder.12 This may be an overestimate of the prevalence of false-positive diagnoses; our referral population may represent patients selected by their physicians as exhibiting atypical presentations or inadequate responses to therapy. Further study in a primary care setting is required to determine the true prevalence of asthma misdiagnosis.

The diagnosis of asthma is based on the presence of symptoms and objective measurements of variable airflow limitation. However, an extensive differential diagnosis of asthma exists.11,13 Some of the alternate diagnosis may be associated with a PC20 greater than 8 mg/mL (ie, some patients with postviral cough) and yet may improve with administration of asthma therapy such as inhaled anti-inflammatory medications. The spectrum of alternate diagnoses given following evaluation by a pulmonary specialist at our center indicates that the incorrect diagnosis of asthma may be due in part to overlapping presentations of asthma and other conditions. The symptoms of asthma include wheezing, cough, and dyspnea that may be present alone or in combination. Indeed, it is well known that chronic cough may be the sole presenting symptom in some asthmatics.14 Rhinitis with postnasal drip, COPD, upper respiratory tract infections, gastroesophageal reflux, and other conditions commonly present with cough and other respiratory complaints.15,16 All of these conditions were present as alternate diagnoses in our study, indicating that, on the basis of history alone, primary care physicians may have difficulty in distinguishing asthma from other conditions. This is consistent with the findings of Pratter et al17 who have shown that clinical evaluation alone may not be sufficient to make a diagnosis of asthma.

An increasing tendency of primary care physicians to diagnose asthma may be responsible for the large number of nonasthmatics being treated with asthma therapy. A survey of trends in the management of asthma indicated a 76% increase in the total prescribing of medications for airflow obstruction between 1970 and 1971 and 1981 and 1982.18 with acceleration of these trends by the late 1980s.19 While increasing prevalence and severity of asthma may contribute to the dramatic rise in asthma medication sales, an alternate hypothesis might be that the significant attention to the problem of underdiagnosing asthma has led to increased awareness of the disease.1-3,6,10 If the rise in asthma diagnosis is partly due to physicians having a high index of suspicion for asthma, it is plausible that there will also be a population of patients receiving asthma therapy inappropriately.

There are several limitations of our data that must be considered. Our study population had a mean age of 40±15 years; generalizing our findings to a younger population may be inappropriate. In addition, our population is likely biased in that more diagnostically difficult cases may have been referred for a specialist’s opinion. Nevertheless, our identification of a large number of patients misdiagnosed as having asthma suggests that with an increasing tendency to diagnose asthma, diagnostic “difficulty” is more common.

The inherent problems in the definition of asthma and in defining criteria for a “negative” methacholine challenge based on 95% confidence limits must also be considered. Such issues have been the focus of considerable debate.13,20-22 It is accepted that most symptomatic asthmatics will have a PC20 of 8 mg/mL or less;10,23-24 however, the methacholine challenge may be reproducible only to within one doubling of the concentration.25 Thus, although lack of responsiveness to methacholine is thought to make the diagnosis of asthma unlikely, widely quoted literature describes a small proportion of patients regarded as having asthma despite having a PC20 greater than 8 mg/mL.20,27 Twelve percent of our patients were diagnosed as having asthma by experienced pulmonologists, despite a “negative” challenge study. Approximately half of
these patients had “borderline” positive methacholine challenges. Methacholine responsiveness of asthmatic patients may vary significantly with medication use, viral illnesses, occupational exposures, and seasonal changes. In our study, treatment with inhaled and oral corticosteroids was not routinely withheld prior to methacholine challenges, and this may have affected the level of airway reactivity. Inhaled budesonide has been shown to give substantial improvements in airway responsiveness; however, only a minority of asthmatic individuals receiving long-term inhaled regimens will return to a normal range.

Misdiagnosis of asthma has many implications, including psychological and financial burdens, potential side effects from use of medications, and morbidity associated with failure to diagnose and treat the true underlying medical condition. To avoid the negative consequences associated with the incorrect diagnosis of asthma, we suggest that primary care physicians do the following: (1) consider common medical conditions that may present with symptoms similar to those of asthma when evaluating patients with respiratory complaints; (2) use spirometry with bronchodilator administration and, when necessary, bronchoprovocation studies more frequently to objectively confirm the diagnosis; and (3) consider referral to specialists when diagnostic uncertainty exists.

REFERENCES