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ORIGINAL ARTICLE

A Population-based Clinical Study of Allergic and Non-allergic Asthma

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Background. The aim of this study was to describe differences between allergic and non-allergic asthma in a large community-based sample of Danish adolescents and adults. **Methods.** A total of 1,186 subjects, 14 to 44 years of age, who in a screening questionnaire had reported a history of airway symptoms suggestive of asthma and/or allergy, or who were taking any medication for these conditions were clinically examined. All participants were interviewed about respiratory symptoms, and furthermore skin test reactivity, lung function, and airway responsiveness were measured. **Results.** A total of 489 individuals had clinical asthma of whom 61% had allergic asthma, whereas 39% had non-allergic asthma. Subjects with non-allergic asthma were more likely to be females, OR = 2.24 (1.32–3.72), $p = 0.003$, and to have cough as the predominant symptom, OR = 1.96, (1.19–3.23), $p = 0.008$, but were less likely to have AHR, OR = 0.40, (0.24–0.66), $p < 0.001$, food allergy, OR = 0.28, (0.11–0.73), $p = 0.009$, and symptoms of rhinitis, OR = 0.08 (0.05–0.14) compared with subjects with allergic asthma. Subjects with non-allergic asthma had had persistent symptoms within the last 4 weeks more often than subjects with allergic asthma (68% vs. 53%), $p = 0.001$. **Conclusions.** Non-allergic asthma accounts for two in every five cases of asthma in adults and constitutes symptomatically, and in terms of lung function, a more severe form of disease than allergic asthma.

Keywords asthma, allergic asthma, non-allergic asthma, atopy, clinical

INTRODUCTION

Since the introduction of intrinsic and extrinsic asthma by Rackeman in 1947, it has been discussed whether these phenotypes represent two distinguishable clinical diseases (1). Recent research shows that from a cellular and immunological perspective intrinsic and extrinsic asthma (henceforth, allergic and non-allergic asthma [2]) have more similarities than differences (3). Conversely, it has been widely accepted that allergic asthma can be objectively distinguished from non-allergic asthma by skin prick test and immunoglobulin E (IgE) levels [2, 4]. For the patient, however, it is not unimportant to distinguish between the two different phenotypes as Rackeman and later Romanet-Manent proposed [1, 2]. Furthermore, Nieves et al. [5] studied the characteristics discriminating allergic from non-allergic asthma and found that patients differed particularly in respect to sex and age at onset.

Most physicians will agree that allergic and non-allergic asthmatics differ with respect to their paraclinical attributes, symptomatology, and need for medical attention and care. However, surprisingly few studies have tried to document this. The aim of this study was consequently to examine whether the two groups in fact show significant clinical differences. We studied an earlier well-described population of adolescents and adults using a wide range of objective tests [6]. We collected data on paraclinical characteristics, classification of disease, and differences in the use of medication in the two groups.

METHODS

Subjects

The study population comprised 10,877 subjects. The subjects were randomly selected from the Danish civil registration list, were 14 to 44 years of age, and were living in urban Copenhagen, Denmark (6). All subjects received a short questionnaire adopted from ACAAI and a total of 5,849 (54%) questionnaires were returned. Subjects who reported at least one symptom suggesting asthma and/or allergy, or were treated for these conditions, were invited to take part in a clinical examination. A total of 1,186 subjects agreed to participate. The examination included an interview, and lung function, airway responsiveness, and skin test reactivity were measured. The Scientific Ethics Committee approved the protocol, and informed consent was obtained from all participating subjects and/or their parents.

Clinical Interview

All participants were interviewed about respiratory and allergic symptoms (in the preceding 4 weeks and at any time in the past) knowledge about self-care, current medication, and smoking habits. Lifetime tobacco exposure was calculated as pack years (tobacco consumption [g/day]/20 × duration of smoking [years]). Height and weight were measured, and body mass index (BMI) was calculated as $(\text{weight (kg)})/(\text{height (m)}^2)$. A respiratory specialist diagnosed and graded the severity of asthma (intermittent, mild, moderate, and severe persistent) according to the Global Initiative for Asthma (GINA) guidelines [7]. In addition, the severity of rhinitis was categorized in accordance with the Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines [8].

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Skin Prick Tests

Skin prick tests (SPTs) were performed using standard dilutions of 10 common aeroallergens. The allergens used were birch, grass, mugwort, horse, dog, cat, house dust mite (HDM) (*Dermatophagoides pteronyssinus* and *Dermatophagoides farinae*), and mold (*Alternaria iridis* and *Cladosporium herbarium*) with positive and negative references being histamine, 10 mg/mL, in 50% glycerol and glycerol, 50%, respectively. The concentrations of allergens were 10 HEP (Soluprick SQ system; ALK Abelló, Denmark). Reactions were read after 15 minutes. A positive result (atopy) was defined as a positive reaction to at least one of the allergens, and a reaction was considered positive if the mean wheal diameter was at least 3 mm. The participants were requested to discontinue medications that contained antihistamines at least 3 days before skin testing. Subjects with asthma concomitantly with a positive skin prick test were regarded atopic.

Spirometry and Bronchial Responsiveness Tests

Spirometry was performed using a dry wedge spirometer and the percentage of predicted normal values was calculated. Airway responsiveness to inhaled methacholine was measured in accordance with the method of Yan et al. [9]. Each aerosol was inhaled starting with saline and followed by increasing doses of methacholine until a cumulative dose of 7.8 μ mol had been reached. The test was terminated when the maximum concentration had been reached or when a 20% decline in FEV₁ had occurred before the end of the dosing regimen. For all subjects experiencing at least a 20% decline in FEV₁ the concentration causing a 20% decrease in FEV₁ (PD₂₀) was calculated. A positive test result, airway hyperresponsiveness (AHR) was defined as a PD₂₀ below 3.9 μ mol.

Statistical Analysis

Data were analyzed using the statistical package SPSS (SPSS Inc., Chicago, IL). Frequencies were calculated and differences between groups were assessed by chi-square tests for categorical data and by *t* tests for normally distributed data. To distinguish allergic from non-allergic asthma logistic regression analysis with backward elimination was performed taking into account the season within which the subjects were being examined.

RESULTS

A total of 489 individuals had clinical asthma. Of these, 296 (60%) were females and the mean age was 29.2 years (see Table 1). Among subjects with asthma, 299 (61%) had allergic asthma, whereas 190 (39%) had non-allergic asthma. In total, 45% of the females with asthma and 30% of the males with asthma were non-atopic. Subjects with non-allergic asthma had on average smoked more and had more often had persistent symptoms within the last 4 weeks. Furthermore, the group with non-allergic asthma had lower lung function and was less likely to be medicated for their disease. On the contrary, airway responsiveness was lower in this group, whereas the degree of airway obstruction was similar in the two groups. Concomitant rhinitis was more often observed in

TABLE 1.—Descriptive characteristics of subjects with allergic and non-allergic asthma in a sample 489 adolescents and adults.

Variable	Allergic asthma (n = 299)	Non-allergic asthma (n = 190)	p value
Demographics			
Sex (female)	54.5%	70.0%	0.001
Age (mean)	28.7	29.7	0.280
BMI (mean)	24.9	24.7	0.750
Smoking (mean packyears)	3.5	5.3	0.025
Symptoms within the last 4 weeks			
Persistent symptoms	52.7%	68.3%	0.001
Objective tests			
AHR	62.9%	48.0%	0.002
LogRDR (mean)	0.68	0.48	0.003
FEV ₁ of predicted	91.4%	88.5%	0.019
FVC of predicted	96.2%	92.5%	0.005
FEV ₁ /FVC	82.0%	81.4%	0.477
Medication*			
SABA	37.1%	25.3%	0.007
LABA	6.7%	1.6%	0.008
ICS	23.1%	15.3%	0.037
Any medication	46.8%	24.8%	<0.001
Concurrent disorders			
Rhinitis	86.6%	31.1%	<0.001
Type 1 diabetes	0.7%	2.7%	0.117
Food allergy	19.0%	5.9%	<0.001
Depression	2.4%	5.9%	0.082
Recurring headaches	13.8%	22.6%	0.015
Recurring sinusitis	9.7%	10.2%	0.876

BMI = body mass index; AHR = airway hyperresponsiveness; LogRDR = logarithm of response-dose-ratio; FEV₁ = forced expiratory volume in 1 second; FVC = forced vital capacity. *Medication taken within the last 4 weeks. SABA = short-acting beta-2 agonist; LABA = long-acting beta-2 agonist; ICS = inhaled corticosteroids.

subjects with allergic asthma, as was food allergy, whereas depression and recurring headaches was more prevalent among subjects with non-allergic asthma. The result of the subsequent logistic regression analysis of the studied variables is shown in Table 2. According to GINA classification subjects with non-allergic asthma had more severe disease compared to subjects with allergic asthma (68% vs. 53% reported persistent asthma within the past 4 weeks). The most prominent symptom in subjects with allergic asthma was wheezing (reported by 39%), whereas subjects with non-allergic asthma more often experienced cough (reported by 52%) (see Table 3).

DISCUSSION

This study showed that in an adolescent and adult population with asthma around 40% have non-allergic asthma. A total of 70% of the subjects with non-allergic asthma are females, whereas the prevalence of allergic asthma is equally distributed between sexes. We found that non-allergic asthmatics in general have more persistent disease than subjects with allergic asthma. The most prominent symptom in

TABLE 2.—Factors that significantly distinguish subjects with allergic asthma from subjects with non-allergic asthma.

Variable	Odds ratio	95% CI	p value
Sex (female)	2.24	(1.32–3.72)	0.003
Cough	1.96	(1.19–3.23)	0.008
AHR	0.40	(0.24–0.66)	<0.001
Rhinitis	0.08	(0.05–0.14)	<0.001
Food allergy	0.28	(0.11–0.73)	0.009

Allergic asthma is reference category in logistic regression analysis. Odds ratios above 1 are in favor of non-allergic asthma and odds ratios below 1 are in favor of allergic asthma.

TABLE 3.—Percentage of subjects with symptoms of asthma according to the GINA classification.

	Allergic asthma (n = 299)	Non-allergic asthma (n = 190)	All (n = 489)
GINA			
1 (Mild intermittent)	47.3	31.7	41.3
2 (Mild persistent)	15.1	15.9	15.4
3 (Moderate persistent)	19.5	28.0	22.8
4 (Severe persistent)	18.1	24.3	20.5
Persistent symptoms	52.7	68.3	58.7
Specific symptoms*			
Cough	36.0	51.9	42.2
Wheezing	39.3	17.9	23.2
Shortness of breath	25.9	31.4	28.0
Chest tightness	21.4	29.8	24.6

*Percentage of subjects with persistent symptoms within the last 4 weeks.

subjects with non-allergic asthma is cough, whereas subjects with allergic asthma more often experience wheezing. Subjects with non-allergic asthma are less likely to have concomitant rhinitis, food allergy, and airway hyperresponsiveness compared with subjects with allergic asthma. Both groups of asthmatics, but in particular subjects with non-allergic asthma, tend to be undertreated according to recommendations.

We found a high prevalence of non-allergic asthma especially among females consistent with previous observations of a higher incidence of asthma, particularly non-allergic asthma, among adult females than among males [10]. On the contrary, we found significantly less rhinitis among subjects with non-allergic asthma compared with subjects with allergic asthma. Around 30% of the subjects with non-allergic asthma had concomitant rhinitis whereas almost 90% of the subjects with allergic asthma had rhinitis. This finding confirms the close connection between allergic asthma and allergic rhinitis [11] and argues against a similar prevalence of rhinitis among the two subgroups of asthma as has been proposed by others [2].

Measurement of serum total IgE, exhaled inflammatory markers and sputum eosinophils would likely have strengthened our conclusions, particularly since we used skin test reactivity as the sole criterion to distinguish between asthma subtypes. It has been claimed that most forms of asthma have allergic features and that non-allergic asthma is not immunopathologically different from allergic asthma [5]. It could therefore be argued that skin test reactivity is too rough a measure to discriminate the allergic from the non-allergic phenotype.

Moreover, follow-up data would have been desirable to be able to address prognostic differences between the two asthma subgroups. It has previously been shown that subjects with non-allergic asthma have a poorer prognosis in terms of lung function compared with subjects with allergic asthma [12]. We found that subjects with non-allergic asthma had on average smoked more than subjects with allergic asthma, which is consistent with previous findings [13]. Also non-allergic asthmatics had significantly lower levels of FEV₁ and FVC and had less airway responsiveness. However, the FEV₁/FVC-ratio was not significantly different between asthma subgroups; neither was the mean age. Cough was the dominant symptom in subjects with non-allergic asthma in contrast to the more classical asthma symptom wheezing, which was the primary symptom among allergic asth-

matics. These findings point towards some over-diagnosis of asthma in non-atopic patients. In particular, early symptoms of chronic obstructive pulmonary disease and chronic mucus hypersecretion in smokers could have contaminated the results [14]. Moreover, since cough is a rather unspecific symptom compared to wheezing and since only 18% of the non-allergic asthmatics had experienced wheezing, some otherwise healthy subjects may have been misclassified as asthmatics and thereby contributed to the differences between groups. However, cough was not the only asthma-defining manifestation in non-allergic asthmatics. The diagnosis of asthma was made by a respiratory specialist on the basis of a global evaluation of the patient who therefore had to have had GINA-specific symptoms at some point to be diagnosed with asthma at the clinical interview. A high occurrence of cough does therefore not, in our opinion, speak against a correct diagnosis of asthma. Rather, smoking in non-allergic asthmatics could have contributed to a different pattern of respiratory symptoms, particularly cough, between these patients. Still, we acknowledge that non-allergic asthma is a difficult diagnosis to make. It would therefore have made our findings more convincing if we for example had performed a reversibility test with short-acting beta-2 agonist. However, this would have interfered with the results of the airway challenge test.

We conclude that non-allergic asthma accounts for around one third of all cases of asthma in adolescent and adult males and around one half of all cases of asthma in adolescent and adult females. Non-allergic asthma is more severe both in terms of lower lung function and in terms of the persistency of symptoms compared with allergic asthma. In addition non-allergic asthma is less often treated sufficiently compared with allergic asthma.

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