
Aspirin intolerance and allergy to house dust mites: important factors associated with development of severe asthma

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Background: Although the occurrence of bronchial asthma is still increasing, the possible factors associated with the development of severe asthma have not been completely determined.

Objective: To measure the incidence of severe asthma and its determinants in outpatients. Aspirin intolerance, house dust mite (HDM) allergy, male sex, age older than 65 years, and duration of asthma exceeding 10 years were investigated as factors potentially related to the severity of asthma.

Methods: The study population included 598 women and 408 men, mean age of 44.59 years (SD $\pm$ 16.45 years), randomly chosen from patients with asthma under follow-up surveillance in an outpatient clinic. Their medical histories were reviewed; spirometry and skin prick tests were performed.

Results: The asthma was diagnosed as intermittent in 35.39%, persistently mild in 33.40%, moderate in 23.76%, and severe in 7.45% of the study cohort. In the patients with atopy, HDM allergy was a significant factor associated with the development of severe asthma [odds ratio (OR) = 5.65]. Of the 1,006 patients, 341 (33.90%) had had asthma for at least 10 years, which was a significant factor in the overall study group (OR = 3.64). We found 95 cases (9.44% of the study group) of aspirin intolerance, including 23 of the 75 patients with severe asthma (30.67%; OR = 5.44). Logistic regression analysis showed that aspirin intolerance was most closely associated with severe asthma (β = 5.79; P < .001).

Conclusions: The data from this study show that aspirin intolerance, HDM allergy, and asthma duration exceeding 10 years are major factors associated with severe asthma in outpatients.

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INTRODUCTION

Asthma is a common condition that is increasing in prevalence. Recent epidemiologic studies performed in urban and rural areas of Lodz Province in Poland showed that 7.7% of adult citizens and 18.3% of children had asthma.¹ Exposure to allergens and hereditary susceptibility are widely accepted as risk factors for development of asthma, but insufficient data are available for a priori identification of the factors associated with severity of the disease.

Bronchial asthma is a major factor in direct and indirect public health costs. Most patients with asthma have a mild to moderate disorder; however, some studies have demonstrated that the 6% of patients who are severely affected are responsible for 52% of the costs associated with asthma,² primarily because of frequent hospitalizations and emergency department treatment. For this reason, identification of risk factors for development of severe asthma is important, so that such patients can be targeted for aggressive therapeutic interventions.

The aim of this retrospective and cross-sectional study was to investigate aspirin intolerance, house dust mite (HDM)

allergy, male sex, age older than 65 years, and duration of asthma exceeding 10 years as potential factors associated with the development of severe asthma.

PATIENTS AND METHODS

Study Subjects

From the adult patients with asthma under follow-up surveillance in the Outpatient Clinic of the Department of Pneumology and Allergy, Medical University of Lodz, 1,200 subjects were randomly chosen for our study group. The mechanism used for this process was a computerized random selection of patients' medical history numbers. Of the 1,200 subjects, 1,006 (83.8%) agreed to participate and completed the cross-sectional part of the study, which ended in the year 2000. An exclusion criterion was the inability to perform acceptable spirometry.

Patients' present and past medical histories were studied. Demographic and clinical data were collected with the use of a questionnaire. Age, sex, aspirin intolerance, smoking, and frequency of other allergic diseases were analyzed. The diagnosis of aspirin intolerance had to be confirmed with a positive result of an inhaled aspirin challenge, which was performed as previously described by Dahlen and Zetterstrom.³ Patients with a history of aspirin intolerance were challenged by inhalation of lysine acetylsalicylic acid. A decline of at least 20% in forced expiratory volume in 1

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second (FEV₁) was regarded as a positive result of the challenge.

The age at onset of asthma was determined as the time of the initial physician's diagnosis of asthma or the onset of symptoms, if recorded earlier. The diagnosis of asthma must have been confirmed by a positive result of a bronchodilation test (change in FEV₁ $\geq$ 12% and no less than 200 mL) or a histamine inhalation challenge (change in FEV₁ $\geq$ 20%). The severity of asthma was diagnosed by clinical judgment, in accordance with the Global Initiative for Asthma guidelines,⁴ on the basis of each patient's latest complaints, results of screening spirometry (FEV₁, forced vital capacity, and peak expiratory flow rate), and use of maintenance and rescue medications. In uncertain cases, the deciding factor defining the degree of severity of the disease was the treatment needed to maintain good control of the asthma.

Procedures

A qualified assistant used the Pneumo RS 2000 spirometer (ABC Med, Krakow, Poland) to perform spirometry during the stable period of asthma in accordance with the American Thoracic Society criteria. The best result of 3 forced maneuvers was used for analysis. Equations used to predict the mean value of pulmonary function measures for sex, age, and height were those proposed by Knudson et al⁵ for white subjects. Before performance of spirometry, inhaled short-acting β_2 -agonists were withheld for at least 8 hours, long-acting β_2 -agonists were withheld for at least 72 hours, and leukotriene antagonists and anticholinergic agents were withheld for at least 24 hours.

Skin prick tests (SPTs) with a set of 8 allergens [*Dermatophagoides pteronyssinus* (Der p), *Dermatophagoides farinae* (Der f), cat, dog, grass, trees, weeds, and feathers] were performed by a technician on the volar surface of each patient's forearm by using 1 lancet for 1 prick.^{6,7} Tests were administered in the morning (between 9 and 11 AM), and results were interpreted after 10 minutes for histamine and after 20 minutes for allergens. A distance of 3 cm was left between the test sites. All wheal sizes were measured as the mean of the longest diameter and the midpoint of the perpendicular diameter. A positive reaction was defined as at least 3 mm greater than the reaction to the saline control. Atopy was defined as having positive results of SPTs to at least one of the tested allergens.

Statistical Analysis

The odds ratio (OR) was used to evaluate the level of risk of developing severe asthma, depending on factors such as aspirin intolerance, HDM allergy (defined as positive results of SPTs to Der p or Der f), male sex, and age exceeding 65 years. In addition, the attributable risk factor was calculated. A multiple logistic regression model was created to allow comparison of the possible effect of studied factors on the severity of asthma. All analyses were performed by using the

Statistica version 5.0 program (StatSoft, Inc, Tulsa, OK). A *P* value less than .05 was regarded as statistically significant.

All subjects gave informed consent to participate in the study and for the aspirin challenge. The design of the study was approved by the local ethics committee.

RESULTS

The study group consisted of 1,006 patients with asthma, who were a mean age of 44.59 ± 16.45 years (range, 18 to 78 years). As shown in Table 1, the study cohort had a preponderance of female patients (59.44%). The asthma was diagnosed as intermittent in 35.39%, persistently mild in 33.40%, moderate in 23.76%, and severe in 7.45% of the study patients. Of the overall group, 789 patients (78.43%) received anti-inflammatory treatment, defined as inhaled glucocorticoids in dosages of at least 400 μ g of budesonide daily or the equivalent or continuous orally administered corticosteroid therapy (Table 1).

In the overall study group, 789 patients (78.43%) had atopy. A statistically significant correlation was found between the severity of asthma and the frequency of positive results of SPTs to Der p, Der f, trees, and grasses (rank Spearman correlation factor: 0.86, 0.81, -0.76 , and -0.92 , respectively; *P* < .05; data not shown).

Data analysis showed that HDM allergy was not associated with the severity of the disease in the overall study group (OR = 0.93). Nevertheless, HDM allergy was a statistically significant factor associated with the development of severe asthma in patients with atopy (OR = 5.65). The attributable risk of developing severe asthma for patients with HDM allergy was 78.64% (95% confidence interval, 60.52% to 96.76%; Table 2). In 341 patients, the duration of asthma had been at least 10 years, which was a statistically significant factor for developing severe asthma in the overall study group (OR = 3.64), in the group of patients with atopy (OR = 3.71), and in those without atopy (OR = 4.58; Table 2).

In the overall study group, 95 cases of aspirin intolerance (9.44%) were found. Of 75 patients with severe asthma, 23 (30.67%) had aspirin intolerance. Statistical analysis revealed that aspirin intolerance was a significant factor associated with the development of severe asthma (OR = 5.44). The attributable risk of developing severe asthma for aspirin-intolerant patients was 25.48% (95% confidence interval, 14.11% to 36.85%; Table 2).

Of the 75 patients (29 men and 46 women) who had severe asthma, 13 (17.33%) were older than 65 years. The OR for developing severe asthma in men and in patients older than 65 years was 0.92 and 1.76, respectively (Table 2). Only 74 patients (7.36% of the overall study group) indicated that they smoked cigarettes.

Multiple logistic regression analysis confirmed the foregoing results. In the overall study group, aspirin intolerance was the factor most closely associated with the development of severe asthma (β = 5.79; *P* < .001; Table 3). In the group

Table 1. Basic Characteristics of the Study Group

Characteristic	No. of patients	Mean $\pm$ SD or % of patients
Age, years	1,006	44.59 $\pm$ 16.45 (range, 18–78)
Sex		
Men	408	40.56
Women	598	59.44
Asthma severity		
Intermittent	356	35.39
Mild	336	33.40
Moderate	239	23.76
Severe	75	7.45
Asthma duration	1,006	8.26 $\pm$ 9.11
≥ 10 years	341	33.90
<10 years	665	66.10
Aspirin intolerance	95	9.44
Patients with atopy (number/study group)	789/1,006	78.43
Intermittent	304/356	85.39
Mild	263/336	78.27
Moderate	169/239	70.71
Severe	53/75	70.67
Anti-inflammatory asthma treatment (treated/study group)*	789/1,006	78.43
Intermittent	219/356	61.52
Mild	280/336	83.33
Moderate	215/239	89.96
Severe	75/75	100
Pulmonary function		
FEV ₁ (% predicted)	1,006	81.37 $\pm$ 25.93
FVC (% predicted)	1,006	86.44 $\pm$ 22.30
FEV ₁ /FVC	1,006	77.25 $\pm$ 18.03

Abbreviations: FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity.

* Treatment described in text.

of patients with atopy, aspirin intolerance ($\beta = 5.44$; $P < .001$), asthma duration exceeding 10 years ($\beta = 3.69$; $P < .001$), and HDM allergy ($\beta = 2.07$; $P = .04$) were also statistically significant factors (Table 4). Logistic regression analysis showed that asthma duration exceeding 10 years was the only significant risk factor in the group of patients without atopy ($\beta = 3.15$; $P = .002$; Table 5).

DISCUSSION

By retrospectively analyzing case histories, we were able to investigate whether aspirin intolerance, age older than 65 years, male sex, asthma duration of more than 10 years, and HDM allergy were potential factors associated with the development of severe asthma. For our investigation, the observational study method was chosen as having some advantages over randomized, prospective trials, including shorter time frames, lower costs, and a heterogeneous group of patients—factors that better characterize the real-life situation. In a recent report, Benson and Hartz⁸ proved that observational studies provide valid information, a finding also confirmed by Concato et al.⁹ Observational studies are a valuable source of information on public health, risk factors, and prognostic indicators. The aim of our investigation was to

identify factors associated with severe asthma in the group of patients encountered in our everyday practice in an outpatient clinic and *not* a group of subjects fulfilling the rigid criteria of a controlled trial. We assumed that use of this approach would provide valuable data.

In our study group, asthma was diagnosed as intermittent in 35.39%, persistently mild in 33.40%, moderate in 23.76%, and severe in 7.45% of cases. This distribution is similar to that found in other studies.^{10,11} Having symptoms of asthma for more than 10 years was a factor significantly associated with the development of severe asthma in the overall study group, as well as in the subgroups of patients with and without atopy. This finding corresponds to results in other studies,^{12,13} in which the duration of asthma was clearly associated with the severity of the disease. Undoubtedly, prolonged inflammation of the airways, which is the central mechanism in the pathogenesis of asthma, leads to remodeling, progressive decline in pulmonary function, increased exacerbation, and increased mortality rate.^{14–16} Early, intensive anti-inflammatory treatment is currently considered the most efficient method for reducing the influence of inflammation on the airways; however, its effect seems to be incomplete. The results of the Childhood Asthma Management

Table 2. Statistical Analysis of Factors Potentially Associated with the Development of Severe Asthma in the Overall Study Group, the Group of Patients with Atopy, and the Group of Patients without Atopy*

Factor	Odds ratio (95% CI)	P value†	Attributable risk (95% CI)
Overall study group (N = 1,006)			
Aspirin intolerance	5.44 (2.47 to 8.41)	<.001	25.48 (14.11 to 36.85)
Asthma duration >10 years	3.64 (1.86 to 5.41)	<.001	47.23 (30.96 to 63.50)
House dust mite allergy	0.93 (0.41 to 1.44)	>.05	...
Age >65 years	1.76 (0.65 to 2.87)	>.05	...
Male sex	0.92 (0.47 to 1.37)	>.05	...
Patients with atopy (n = 789)			
Aspirin intolerance	8.93 (2.59 to 15.27)	<.001	31.58 (17.58 to 45.58)
Asthma duration >10 years	3.71 (1.35 to 6.07)	<.001	47.03 (26.03 to 68.03)
House dust mite allergy	5.65 (1.11 to 10.19)	<.001	78.64 (60.52 to 96.76)
Age >65 years	0.51 (–0.52 to 1.52)	>.05	...
Male sex	0.78 (0.73 to 0.83)	>.05	...
Patients without atopy (n = 217)			
Aspirin intolerance	2.98 (–0.77 to 6.73)	>.05	...
Asthma duration >10 years	4.58 (1.02 to 8.14)	<.001	47.72 (17.05 to 78.39)
Age >65 years	1.87 (–0.4 to 4.14)	>.05	...
Male sex	1.13 (–0.02 to 2.28)	>.05	...

Abbreviation: CI, confidence interval.

* Boldface entries denote statistically significant results ($P < .05$).

† χ^2 test.

Table 3. Results of Logistic Regression Analysis for the Overall Study Group (N = 1,006)*

Factor	Asthma duration >10 years	Aspirin intolerance	Age >65 years	HDM allergy	Male sex
β	4.64	5.79	–0.31	0.08	0.18
P	<.001	<.001	.75	.93	.86

Abbreviation: HDM, house dust mite.

* Boldface entries denote statistically significant results ($P < .05$).

Table 4. Results of Logistic Regression Analysis for the Group of Patients with Atopy (n = 789)*

Factor	Asthma duration >10 years	Aspirin intolerance	Age >65 years	HDM allergy	Male sex
β	3.69	5.44	–1.16	2.07	–0.18
P	<.001	<.001	.24	.04	.85

Abbreviation: HDM, house dust mite.

* Boldface entries denote statistically significant results ($P < .05$).

Table 5. Results of Logistic Regression Analysis for the Group of Patients without Atopy (n = 217)*

Factor	Asthma duration >10 years	Aspirin intolerance	Age >65 years	Male sex
β	3.15	1.21	0.14	1.19
P	.002	<.23	.89	.24

* Boldface entries denote statistically significant results ($P < .05$).

Program¹⁷ showed that neither budesonide (200 μ g, twice daily) nor nedocromil (8 mg, twice daily) was better than placebo for protecting against the decline of pulmonary function in a group of children with mild-to-moderate asthma. Budesonide treatment resulted in better control of asthma and reduction of airway hyperresponsiveness than did use of placebo or nedocromil.

Our study revealed that HDM allergy and aspirin intolerance are factors associated with the development of severe asthma. HDM and cockroach allergens are 2 of the most common household factors responsible for IgE-mediated diseases. Rosenstreich,¹⁸ who studied household allergens, found a relationship among HDM sensitization, allergen levels, and asthma severity and related morbidity in children. Similarly, Squillace et al¹⁹ proved that, in an area with a high prevalence of asthma and where most houses contain high concentrations of dust mite allergen, HDM sensitization is the strongest risk factor responsible for the development of asthma. In addition, Peat et al²⁰ demonstrated that a clear correlation exists between Der p I exposure and airway hyperresponsiveness. Convincing evidence indicates that avoidance of HDM allergens can effectively reduce allergic symptoms.²¹ Attributable risk factor is a statistical parameter

showing the possible effect of avoiding the studied risk factor. In our group of patients with atopy, the attributable risk factor for the HDM allergy was 78.64%. This finding supports HDM avoidance as a useful intervention to diminish the severity of asthma.

In contrast, avoiding aspirin does not prevent progression of the inflammatory disease,²² although it does prevent aspirin-induced life-threatening reactions. Characteristically, aspirin-intolerant patients have asthma, recurrent nasal polyps or chronic hypertrophic sinusitis, and a history of bronchoconstriction or other generalized symptoms after administration of aspirin or aspirin-like drugs. Aspirin intolerance affects approximately 10% of patients with asthma and is associated with a moderate or severe course of the disease. This association has been confirmed by data from our study. Of our overall study group, 9.44% experienced aspirin intolerance, and aspirin intolerance was found to be a strong factor associated with the development of severe asthma. Typically, aspirin-intolerant patients with asthma are thought not to have atopy.^{22,23} In our study group, however, most aspirin-intolerant patients had atopy (69.4%; data not shown), a finding that may simply reflect the increase in the number of patients with atopy in our society. Persistent eosinophilic inflammation is the key mechanism in the pathogenesis of aspirin intolerance.²⁴ We still do not know which factors are responsible for the persistence of this process—and, as a result, for the severity of asthma—in patients who avoid the triggering factors of aspirin and aspirin-like drugs. Only intensive treatment of asthma and sinusitis or aspirin desensitization can result in a decrease in the severity of asthma.²²

We have observed that the problem of smoking among patients with asthma still exists. Some studies have shown that even 60% to 70% of patients with asthma smoke cigarettes.²⁵ In the current study, smoking habit was recorded in only 74 cases (7.36% of the overall study group). This finding may have been attributable to withholding of information about smoking and to suboptimal wording of the questionnaire. The question “Do you smoke?” should have been replaced by “How much do you smoke?” In our everyday medical practice, we have subsequently noted that this manner of inquiring about smoking yields much more reliable information.

CONCLUSION

The data from this study highlight the risk factors associated with the development of severe bronchial asthma. These findings suggest opportunities to promote improvement in the course of asthma by addressing those factors significantly associated with greater severity of the disease.

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