
Prognostic Factors of Severe Asthma in Puerto Rico.

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Asthma in Puerto Rico is a serious Public Health Problem. This study extends our cross-sectional self-reported asthma prevalence survey of 3,000 volunteers. The purpose of the present study was to analyze the importance of known prognostic factors of asthma severity among 486 self-reported participants. Patients with more than one visit to the emergency room in the previous 12 months due to asthma exacerbations were classified as cases of "severe asthma", and those asthmatic patients who did not visit emergency rooms were classified as "non-severe asthmatic subjects". Severe cases and non-severe asthmatic subjects were compared regarding age, sex, family history of asthma, presence of household pets, and in the previous 12 months: history of hospitalization due to asthma, respiratory infections, tobacco smoking, exposure to passive smoking, and avoidance of passive smoking. Crude and logistic regression adjusted odds ratio was used as a measure of association between each prognostic factor, and the outcome namely severe asthma, while adjusting for all confounders simultaneously. The

results clearly showed that previous hospitalizations due to asthma (OR=7.3, $p<0.0001$) and frequent of respiratory infection (OR=2.5, $p=0.0003$) were prognostic factors associated with increased asthma severity. A statistically significant, two percent less likelihood to have severe asthma for each year of age was found. Weak associations were found between asthma severity and male gender, family history of asthma, passive smoking, and presence of household pets. Avoidance of environmental tobacco exposure (passive smoking) was found to be an important and statistically significant protective factor associated with a 47% less likelihood for severe asthma. In conclusion, appropriate management of patients with history of hospitalization due to asthma is very important. The correct management of respiratory infection in asthmatic patients may result in a reduction of up to 60 percent of the odds of having asthma severe enough to require emergency treatment, and may reduce by 86.3 percent hospitalizations.

Key words: Prognostic factors, Asthma, Puerto Rico.

The seriousness of asthma in public health is evidenced by the fact that the morbidity and mortality of the disease in the United States is increasing (1). Mortality is increasing at a rate of 10.1 percent annually in children 5 to 14 years of age, and it now affects more children in the 0-14 year age range in the Puerto Rican and African American communities than in

any other group (2,3). In 1989 a prevalence of asthma of 31.9 per 100 school-age children was reported in Puerto Rico (4). In contrast, the prevalence of asthma in Puerto Rican children of the same age but living in the Continental United States was reported to be only 11.2 per 100 children. Prevalence in all of the children in the United States was 5 per 100 children for 1989 (5).

Ten years after this study the prevalence of asthma in Puerto Ricans living in Connecticut was 18.4 per 100, 11.3 among African Americans, and 7.4 among non-Hispanic whites (6). In addition to the importance of these data with respect to susceptibility of asthma, is the financial burden that affected families must face. In the United States, a middle class family could spend up to one-third of their income on the treatment and management of an asthmatic child (7). Asthma research in Puerto Rico is a high priority, but very little has been published, even though the prevalence is thought to be high. The purpose of the present study was to analyze the importance of selected risk factors as predictors for asthma severe

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enough to require a visit to the emergency department per year in Puerto Rican asthmatics.

Methods

A cross-sectional survey was conducted in 3,000 volunteers with a standardized 37 item questionnaire. This instrument was previously tested by a pilot study in 50 individuals. The percent agreement and kappa statistics were calculated to assess the reliability of each question of the instrument. The survey was applied to persons entering, through the main entrance, to a new mall in Ponce, Puerto Rico during three consecutive weekends until the 3,000 individuals sample size was reached. Among the subjects that were approached for interview, 97 percent chose to participate in the survey.

Study participants that answered positively to a series of standardized diagnostic questions related to physician diagnosis, the signs, symptoms, and treatment of asthma were classified as asthmatics. This self-reported diagnostic instrument was applied following the recommendations of Abranson and Burney (8,9). The field methods are explained in more detail in a previous publication of this survey in which the point prevalence, demographic distribution, and seasonality of asthma were reported (10). In this cross-sectional study, 486 self-reported asthmatic participants out of the 3,000 volunteers of the original survey were included. For the study of prognostic factors, to avoid intra-family correlation, only one asthmatic was included from each family with more than one asthmatic. Participants diagnosed with asthma for more than two years were classified as cases of asthma. Cases of asthma that visited the emergency room in the previous 12 months due to asthma were classified as "severe asthmatic individuals" and those asthmatic subjects who did not visit emergency rooms in the previous 12 months due to asthma exacerbations were classified as non-severe asthmatic subjects. Severe and non-severe asthmatics were compared regarding age, sex, family history of asthma, presence of household pets, and in the previous 12 months: hospitalization due to asthma, upper respiratory infections, cigarette smoking, exposure to passive smoking, and avoidance of passive smoking. The crude and the adjusted odds ratio were used as measures of association between each prognostic factor and the outcome severe asthma. The chi-square or Fisher's exact tests were used to assess the statistical significance of the crude odds ratio (11). Interaction and confounding were explored by using Mantel-Heanszel stratified analysis and no important or statistical significant interaction were found (12). Age was analyzed as both continuous and as a categorical variable. Multiple logistic regression was used for the

adjusted analysis in which the association of each independent variable was studied adjusting for all potential confounders simultaneously (13,14).

Results

A total of 273 patients visited the emergency department in the previous 12 months (severe cases), whereas 213 did not (non-severe asthmatics). The group of severe cases was 4.6 years younger than the non-severe patients ($p = 0.0049$). Sixty percent of the severe cases were younger than 20 years of age while 46 percent of the non-severe patients were found on that age group (Table 1). A 14.3% of the severe cases were found in the 30-39 years old group while 18.8% of the non-sever patients were in that age group. The rest of the age group distribution was similar between severe and non-severe study participants (Table 1).

Table 1. Age distribution of subjects that visited the emergency room due to asthma in the 12 months before the interview (severe cases) and those that did not (Non-severe asthmatic subjects).

AGE GROUP	Severe Cases ER VISITS (+)	Non-severe asthmatic subjects ER VISITS (-)	TOTAL
0 - 9	45 (30.4)	83 (21.1)	128 (26.3)
10 - 19	81 (29.7)	53 (24.9)	134 (27.6)
20 - 29	39 (14.3)	40 (18.8)	79 (16.3)
30 - 39	34 (12.5)	30 (14.1)	64 (13.2)
40 - 49	20 (7.3)	20 (9.4)	40 (8.2)
50 - 59	8 (2.9)	19 (8.9)	27 (5.6)
60 - +	8 (2.9)	6 (2.8)	14 (2.9)
TOTAL	273 (100)	213 (100)	486 (100)

Mean age difference between severe cases (20.41, $s = 16.04$) and non-severe asthmatic subjects (25.01, $s = 16.28$): 4.6 years, $p = 0.0049$

Statistically significant associations with severe asthma were found for: previous hospitalization, frequent respiratory infections, avoidance of passive smoking, smoking, and increasing age. Severe asthma cases were hospitalized 7.3 times more frequently than non-severe asthma patients. The odds for frequent respiratory infections were 2.5 times higher among severe cases than among non-severe patients. Avoidance of passive smoking was found to be protective. Those that avoid passive smoking have 47 percent less chance to have severe asthma (OR = 0.53). Smoking was found inversely related to severe asthma. Those that smoke are 53 percent less likely to have severe asthma (Table 2). In Table 2, it can be seen that the likelihood of having severe asthma decreases about 2 percent with each year of age (as found applying multiple adjustment procedures with logistic regression OR = 0.98, $p = 0.016$). Age was also analyzed as a categorical variable but no association was found with

Table 2. Crude and adjusted association (multiple logistic regression) of prognostic factors and severe asthma as assessed by comparing severe cases and non-severe asthmatic subjects.

Prognostic factor	Severe cases	Non-severe asthmatic subjects	Crude OR (95% C.I.)	Adjusted OR (95% C.I.)	p-value
Hospitalization					
Yes	252	135	6.9 (4.1-11.9)	7.3 (4.2-12.6)	0.0001
No	21	78			
Frequent respiratory infections					
Yes	237	150	2.8 (1.7-4.5)	2.5 (1.5-4.1)	0.0003
No	36	63			
Avoidance of passive smoking					
Yes	80	84	0.64 (0.44-0.93)	0.53 (0.34-0.83)	0.0059
No	193	129			
Smoking					
Yes	15	24	0.46 (0.23-0.90)	0.47 (0.22-0.97)	0.0439
No	258	189			
Passive smoking					
Yes	140	94	1.3 (0.93-1.9)	1.3 (0.82-1.9)	0.2894
No	133	119			
Family history					
Yes	169	138	0.88 (0.61-1.3)	0.82 (0.54-1.3)	0.362
No	104	75			
Gender					
Male	105	71	1.3 (0.86-1.8)	1.1 (0.77-1.7)	0.5031
Female	168	142			
Household pets					
Yes	152	109	0.9 (0.62-1.3)	0.9 (0.59-1.3)	0.5675
No	141	104			
Age					
(Each year)			0.98 (0.97-0.99)	0.98 (0.97-0.99)	0.0161

Note: All associations were adjusted by age, gender, and/or other confounders simultaneously by using multiple logistic regression analysis

severity in spite of the significant difference in the mean age between severe and non-severe cases found during the crude analysis.

Environmental tobacco exposure, passive smoking or ETS, presence of household pets, family history of asthma, and gender differences between severe and non-severe patients were not found importantly associated with severity nor statistically significant ($p > 0.05$).

Discussion

In recent years, information regarding asthma in Puerto Rico is slowly emerging. These reports strongly suggest that asthma is an important public health concern in the

Island due to its high prevalence. However, the characteristics of the asthmatic population and the natural history of this disease in Puerto Rico remain to be defined. Knowledge of these two important aspects of the disease may facilitate the development of accurate prognostic tools to determine the severity of the disease leading to future hospitalizations, and to implement adequate prevention, treatment and management of this condition. Since it is possible that risk and prognostic factors vary from region to region specially related to the environmental triggers, it is important to study the local asthmatic population emphasizing on their particular characteristics. The present report stems from a previous study conducted in the city of Ponce, Puerto Rico in which a cross-sectional study of

self-referred asthma and its severity was estimated (10). It is important to note that the present study has limitations. Information was collected by means of a short interview and no validation of diagnosis was conducted by a physical examination or through medical records. Thus, there is a potential for misclassification error of exposure and disease (9). Since the severe vs. non-severe classification was carried out during the data analysis (and not before or during the interview), misclassification is likely to be non-differential. Therefore, an underestimation of the associations may be present in the results of this study (13).

Little is known about the prognosis of severity for asthma, however, there are several factors that can be considered to have a prognostic value for asthma. These include male gender, history of respiratory infections, atopy and active cigarette smoking or environmental tobacco exposure (ETS), and positive family history (15-18). The present study emphasizes on selected prognostic factors of asthma severity including hospitalizations due to asthma exacerbations in the previous 12 months, presence of respiratory infections in the last 12 months, active cigarette smoking in the last 12 months, exposure to cigarette smoke, family history of asthma, gender and presence of house pets. Most of these risk factors have been described as common triggers for asthma worldwide (14,15). Of the prognostic factors studied, only two of these had significant associations; previous hospitalizations due to asthma and respiratory infections in the last 12 months.

Hospitalizations due to asthma in the previous 12 months was found to be the most important indicator of severe asthma and was reported to be over seven times higher among severe asthmatics than in non-severe asthma patients (OR = 7.3, 95% CI: 4.2-12.6), this association was higher than those reported for the same indicator elsewhere (19). This finding has special importance because it has been estimated that in the United States, the cost of illness related to asthma for 1990 was \$ 6.2 billion U.S. dollars. The value of reduced productivity and loss of school days represents the largest single indirect cost, approaching one billion dollars a year. In fact, 43% of the economic impact of asthma is associated with emergency department use, hospitalization and death.

Since we have found that previous hospitalization is a significant indicator of asthma severity, it is possible that special efforts to improve asthma management in severe cases maybe able to reduce hospitalization to a level experienced by the asthmatic non-severe asthmatic subjects, that is 86.3% less (Table 2) (9,13). Therefore, by improving management of severe asthma, substantial savings in direct and indirect costs of asthma could be

achieved by concentrating specialized intervention and case management in those patients who have ever been hospitalized due to asthma.

In the population studied, a history of frequent respiratory infections increased the likelihood of an asthma attack in the previous 12 months by 2.5 times. This observation is in agreement with previous publications indicating that respiratory infections are one of the most common causes of asthma exacerbation for patients of all ages (20,21). Viral infections such as rhinoviruses, coronaviruses, influenza B, respiratory syncytial virus, parainfluenza virus, and chlamydia are triggers for asthma exacerbations which increase the severity of this condition. Although the epidemiology of respiratory viral infections in the tropical environment of Puerto Rico is unknown, there is some evidence that these pathogens may affect the severity of asthma. In a previous report we were able to demonstrate that asthma hospitalizations in Ponce have a peak in the winter months (22). This variation in the asthma attacks requiring hospitalizations may be indicative that exacerbations are triggered by biological agents such as virus, endotoxins produced by bacteria and domestic mites. In addition, the hospitalized asthmatics had a high percentage of upper and lower respiratory infections as underlying conditions for asthma hospitalizations. It is possible that viruses, specially rhinoviruses may be important contributors for the high prevalence of asthma in Puerto Rico since 85% of the asthmatics are individuals suffering atopy (23). This allergy (atopy) among the asthmatic population in Puerto Rico may be a prognostic factor since it has been demonstrated that atopic individuals may be predisposed to more severe viral respiratory infections worsening their asthma (24,25). Considering the fact that asthma hospitalizations have a seasonal trend, and that a high percentage of the asthmatics are sensitized to domestic mites, a possible interaction between these factors may contribute to the severity of asthma in the Puerto Rican asthmatics.

An important but controversial risk factor for the development of asthma is a positive family history of asthma (26). Others report that family history of asthma may increase the susceptibility to develop asthma by 2.5 times (6). However, family history of asthma as a prognostic factor for severity may not be important in the Puerto Rican population as our data showed only a weak and non-statistically significant association between a family history of asthma and severe asthma in this study.

Tobacco smoking is a known risk, and prognostic factor associated with asthma development and exacerbation for over 40.5 percent of the individuals affected in the population (population attributable risk = 40.5%) (27). In

the present study, the tobacco smoking rates were much lower, as only 5% of the severe asthmatics reported to have smoked in the last 12 months as compared to 12% of the non-severe asthmatic group. The cross-sectional nature of the present study makes it impossible to elucidate the temporal relationship of the associations. Although smoking is an important risk factor for severe asthma, our findings may suggest that, in our population, the severity of the disease may influence asthmatics to decrease the amount of tobacco smoked or to stop smoking completely. It is possible that asthmatic subjects who are able to smoke without serious consequences may continue to smoke. This situation may more often be seen among mild cases of asthma than among severe cases. Exposure to ETS or passive smoking has been regarded as an important risk factor for asthma (28). Although we found such exposure to be a weak prognostic factor for severe asthma, avoidance of exposure to ETS was found to be an important and statistically significant protective factor associated with a 47% reduction of the risk for severe asthma. This finding is of importance since it suggests that in Puerto Rico, asthmatics should be aware of the effects of ETS on their asthma, and take action to prevent exposure to ETS. In fact, the data shows that only 29.3% of the severe asthmatics avoid ETS. Clearly, this percentage is low to cause an overall impact on the incidence rate of severe asthma. Therefore, special attention should also be given to reduce ETS in severe asthmatics in spite of the poor overall impact on the asthmatic population.

Gender differences in our study population were found to be consistent with other studies in which males were found to have a higher prevalence of severe asthma and a worst prognosis of the disease (29). In our study, we only observed a slight association which was not statistically significant, as only 25 percent more risk for males resulted in the crude analysis (OR = 1.25), and a 13 percent more risk was found after multiple adjustment procedures (OR = 1.13). This OR is somewhat lower than that reported in other studies conducted in children, which showed that the risk of severe asthma in males is 1.7 times higher than in females. In recent years, information regarding asthma in Puerto Rico is slowly emerging. These reports strongly suggest that asthma is an important public health concern in the Island due to its high prevalence.

It is well established that young age is one of the most important prognostic factors for asthma (30). In the Puerto Rican population, our results confirm that the prevalence of severe asthma decreases with age. It is important to note that in the present study, the risk decreases by two percent (2%) per year of age as compared with other populations in which the reported decrease in asthma per year in children 7-14 years of age was 15 percent

(31). This suggests that the factors that cause tolerance to allergenic environmental irritants with increasing age may not be as important in Puerto Rico as in other ageing populations.

It is well documented that pet allergens are important contributors to allergic asthma. Pet ownership can place individuals at considerable risk of asthma exacerbations, since at least 50 percent of homes own either a dog or a cat (32) and this may be a significant factor associated with asthma severity (33). Cat allergen exposure, in particular is strongly associated with hospitalizations for asthma as previously reported (34). In the present study, we found no association between severe asthma and pet ownership. Other authors have also reported lack of association between asthma and the presence of household pets (25). In our study, this lack of association may be explained by the cross-sectional nature of our data. No questions were asked about past exposure to pets, or the reasons why the subjects did or did not keep pets. Asthma subjects that have pets may be those who know that they do not suffer exacerbations of asthma when pets are present. Alternatively, this lack of association may also indicate that other factors that are not included in the study may be confounding the association.

In conclusion, hospitalization in the preceding 12 months was reported to significantly increase the risk of severe asthma compared with control asthmatics. Therefore, proper asthma control in severe cases may be able to reduce hospitalizations up to 7 times (86.3% less frequently) (9,13). In addition, a history of frequent respiratory infections was found to be significantly associated with severe asthma, and was the second most important prognostic factor associated with severe asthma after adjustment for age, gender and all other potential confounders simultaneously. Proper management of respiratory infection in asthmatic subjects may reduce up to 60 percent the risk of having asthma severe enough to require emergency treatment. These data show that it is of critical importance to conduct an epidemiological study on severe asthma and to determine the role of respiratory infections as risk factor for severe asthma in Puerto Rico.

Resumen

Este estudio se extiende de uno transversal de prevalencia de asma que fue realizado por medio de una encuesta a 3,000 voluntarios. El propósito de este estudio fue analizar la importancia de los factores que pronostican la gravedad del asma entre 486 asmáticos. Los pacientes que visitaron más de una vez la sala de emergencia en los pasados 12 meses debido a exacerbación de asma, se clasificaron como casos de "asma grave", y aquellos

pacientes que no visitaron la sala de emergencia fueron clasificados como Asujetos con asma no graves@. Los casos graves y los no graves se compararon de acuerdo a edad, sexo, historial familiar de asma, presencia de mascotas en el hogar; y en los pasados 12 meses: historial de hospitalización por asma, infecciones respiratorias, fumar, exposición al humo del cigarillo (fumador pasivo), o si evitó estar expuesto al humo del cigarillo. Los OR ajustados se utilizaron como medida de asociación entre cada factor pronóstico. Los resultados demostraron claramente que las hospitalizaciones previas por asma (OR=7.3, $p<0.0001$) y la frecuencia de las infecciones respiratorias (OR=2.5, $p=0.0003$) fueron factores pronósticos asociados con el incremento en la gravedad del asma. Como hallazgo estadísticamente significativo, se encontró que un 2% fue menos propenso a desarrollar asma severa por cada año de vida. Se encontró poca asociación entre la severidad de asma con pertenecer al género masculino, tener historial familiar de asma, ser fumador pasivo, y tener mascotas en el hogar. Se encontró que el evitar estar expuesto al humo del cigarillo, es un factor de protección que ha sido estadísticamente significativo y ha sido asociado con un 47% de menos probabilidad de contraer asma grave. En conclusión, el manejo apropiado de los pacientes con historial de hospitalización por asma es muy importante. El manejo correcto de una infección respiratoria en pacientes asmáticos puede reducir hasta un 60% la probabilidad de padecer asma que sea tan grave como para necesitar tratamiento de emergencia, y puede, además, reducir un 86.3% de las hospitalizaciones.

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