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The Link between Uncontrolled Asthma and Sensitization to Inhalant Allergens: Evidence from Jeddah, Saudi Arabia

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Abstract

Background: For optimal asthma control, current guidelines recommend the assessment of allergy phenotype. This study investigates the relationship between asthma control and sensitization to inhalant allergens.

Methods: A cross-sectional study was conducted over a one year period since January 2011. Asthmatics were sequentially selected from allergy clinic at King Abdulaziz University Hospital in Jeddah. Evaluation of asthma control was based on GINA guideline. Assessment of the sensitization towards inhalant allergens was measured *in-vivo* by wheal size and number of positive reactions on the standard skin prick test (SPT). SPSS was used to analyse any statistical correlation.

Results: A total of 110 asthmatics with a mean age of 34 ± 14 years were included, 63.6% being females. Asthma was predominantly uncontrolled in 68 cases (61.8%), partly controlled in 26 cases (23.6%) and controlled in 16 cases (14.5%). SPT to common inhalant allergens was positive in 76 asthmatics (77.6%); of which 54 (55.1%) were uncontrolled, 13 (13.3%) partly controlled and only 9 (9.2%) were controlled asthmatics. The predominant allergens were Dermatophagoides pteronyssinus in 57 cases (54.8%), Dermatophagoides farinae in 49 cases (47.1%), cat epithelia in 35 cases (33.7%) and cockroach in 23 cases (22.1%). Uncontrolled asthma was correlated significantly with positive SPT (p=0.038).

Conclusions: More than half of the uncontrolled asthmatics population is sensitized to indoor inhalant allergens. This clinically favours the assessment of allergic status in any asthmatic, whose symptoms are not controlled. This is one of the early studies exploring the potential link between asthma control and sensitization to inhalant allergens.

Keywords: Allergens; Asthma control; House dust mite; Sensitization; Skin test

Abbreviations: BHR: Bronchial Hyper-Responsiveness; EPR: Expert panel report; FEV1: Forced Expiratory Volume in one second; GINA: Global Initiative for Asthma; HDMs: House Dust Mites; IgE: Immunoglobulin E; KAUH: King Abdul Aziz University Hospital; NAEPP: National Asthma Education and Prevention Program; PEF: Peak Expiratory Flow; SD: Standard Deviation; SPT: Skin Prick Test

Introduction

Asthma is a common chronic inflammatory condition of the airways, characterized by variable and reversible symptoms related to airflow obstruction, bronchial hyper-responsiveness (BHR), and airways inflammation [1].

About 300 million people worldwide have asthma, with the highest prevalence in the UK, Australia and North America [2]. In Saudi Arabia, the prevalence of asthma is higher than in other Arab countries and Europe; with substantial regional variations [3]. Asthma prevalence is rising significantly in Saudi adults and children [4]. Control of asthma is a major concern among the Saudi population; a recent asthma control survey revealed predominance of uncontrolled asthmatics [5].

Asthma has many phenotypes [6]. Allergic asthma is the predominant phenotype and is immunologically mediated by Immunoglobulin-E (IgE) antibodies through sensitization against common inhalant allergens such as house dust mites (HDMs), animal dander, pollens and moulds [1,7]. Several *in-vivo* and *in- vitro* allergy tests can be performed to measure the titre of IgE antibodies (sensitization) in allergic asthma [8].

National and international guidelines recommend asthma management based on clinical control assessment rather than severity (SINA, GINA, NAEPP). Asthma control can be well monitored at all stages in a clinical setting with defined characteristics for controlled, partially controlled, and uncontrolled asthma [9-11].

In the past, several studies have delved into the clinical correlation between sensitization to common inhalant allergens and the severity of asthma [12-14]. Koshak conducted a similar study in the city of Jeddah, Saudi Arabia [15]. However, none of the previous studies have explored the relationship between sensitization to common inhalant allergens and asthma control; particularly in the light of recent medical practice guidelines and in the light and context of the Saudi population.

In order to fulfill this unexplored research area, we conducted this study to explore the relationship between clinical asthma control and IgE-mediated sensitization to common inhalant allergens among asthmatic patients in the Saudi population and within the context of recent clinical practice guidelines.

Methods

Study population

This cross sectional study was conducted at the allergy clinic in King Abdulaziz University Hospital (KAUH) at Jeddah, Saudi Arabia.

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This study was performed over a one year period starting from January 2011. The study included adults and children diagnosed with bronchial asthma who presented to the allergy clinic at KAUH during this period. Pregnant and lactating women were excluded for safety reasons. Smokers have been excluded to rule out the likelihood of chronic obstructive pulmonary disease; acting as a potential confounder of results and to restrict the study population exclusively to asthmatics only. Patients with suspected occupational asthma were also excluded to avoid confounding occupational etiology.

Global Initiative for Asthma (GINA) guideline 2011 was adhered to for the evaluation of asthma control. The clinical parameters chosen for for assessment of the asthma control were: diurnal symptoms, nocturnal symptoms, limitation of activities, need for relievers or rescue medications, presence of exacerbations and measurement of peak expiratory flow (PEF) or forced expiratory volume (FEV1) at the clinic visit. Accordingly, patients were classified into three groups: controlled, partly controlled and uncontrolled asthma. Asthmatics were allocated to a particular group based on their clinical parameters status.

The study protocol was approved by the local research ethics committee at KAUH.

Data analysis

A descriptive analysis approach was used for the characterization of the study population. Continuous variables were expressed as the mean ± standard deviation (SD): age, number of associated comorbid diseases, number of positive inhalant allergens, wheal diameter of skin test reactivity, IgE serum level and eosinophil count.

Categorical variables were described by the number and percentage of patients in each category (gender, baseline characteristics, asthma control status, characteristics of asthma control, comorbid-associated diseases, and sensitization to inhalant allergens).

For bivariate analysis, the Chi-square test was used to compare qualitative variables and the t-test was used to compare two means. Spearman correlation analysis was used to measure the association between sensitization to inhalant allergens and asthma control level.

All data were categorized and analyzed using the Statistical Package for the Social Sciences (SPSS Inc., Chicago, IL, USA) for Windows Release 16.0. p values less than 0.05 were considered statistically significant.

In-vivo assessment

Sensitization to inhalant allergens was determined by evaluating the results of skin reactivity after 15 minutes in a standard skin prick test (SPT). The panel of inhalant allergen extracts (Alyostal®) appropriate for the SPT was obtained from Stallergen (France).

The following inhalant allergens were examined: Mites including Dermatophagoides pteronyssinus (Dp), Dermatophagoides farinae (Df) and Blomia tropicalis (Bt); Cockroach: Blattella germanica (German cockroach); Animal dander: Cat epithelium (Felis domesticus) and dog epithelium (Canis familiaris); horse hair, and feather dander. Pollens: Timothy grass (Phleum prat.), Bermuda grass, Rye grass, Mugwort (Artimisia vulg.), Plantain, Salsola kali (Russian Thistle), Chenopodium alb (Fat hen), Date Palm, Mesquite (Prosopis), Amaranthus Retro, Mimosa (Acacia deal), Oleaceae; and Moulds: Candida, Cladosporium, Alternaria alternata, Aspergillus mix, fusarium and Penicillium mix.

Patients were advised to stop oral antihistaminic drugs at least 7 days prior to sensitization testing. They were also advised to avoid application of creams and moisturizers on forearms to decrease the chance of allergen extract droplets running into each other. For patients who were on oral steroids continuously for more than two weeks, the SPT was performed three weeks after the therapy had been stopped [16].

SPT was carried out on the forearm, however the back was used occasionally in children. A single drop of each allergen extract was applied, two centimetres apart after sterilization of skin with alcohol. A skin-prick was performed within the allergen drops with Stallerpoint plastic needles (Stallergen, France).

A wheal reaction after 15 minutes ≥ 3 mm in diameter more than negative control was regarded as a positive sensitization to that allergen.

Results

A total of 110 asthmatics met the inclusion criteria and their data was analyzed. Of these, 41 (36.4%) males and 69 (63.6%) female patients completed the study. Patients' age ranged between 3-76 years with a mean of 34 ± 14 years. The total number of patients with controlled asthma was 16, which represented 14.5% of the study population. A notably higher number of patients (n=68) suffered from uncontrolled asthma (61.8%) followed by partly controlled asthma reported in 26 patients (23.6%). The mean age for the uncontrolled asthmatics was 32 ± 14 years whereas mean age values among partly controlled and controlled asthmatics were 35 ± 14 and 40 ± 16 years respectively. However, this age variation was not statistically significant (p=0.172) (Table 1). Out of 110 asthmatics, 99 cases, which represent 90%, have a history of association of other common allergic diseases. Allergic rhinitis was the commonest associated allergic disease (82.7%) (Table 1).

SPT reactivity in study subjects

SPT was performed to 98 asthmatics (89%). SPT was positive to one or more inhalant allergens in 76 patients (77.6%). The mean number of positive inhalant allergens among the three subgroups of asthmatics in this study was as follows: controlled asthmatics 2.9 ± 3.5, partially controlled asthmatics 2.2 ± 2.5 and 3.3 ± 2.9 in uncontrolled asthmatics; with predominance of positive SPT in uncontrolled asthmatics accounting for 54 cases (55.1%). A statistically significant correlation was noted between positive SPT results and asthma control (p value=0.038) (Table 2).

The prevalence of positive sensitization was highest for HDMs, cat and German cockroach as follows: Dermatophagoides pteronyssinus 57 cases (54.8%), mean wheal diameter (3.49 ± 3.53 mm); Dermatophagoides farinae 49 cases (47.1%), mean wheal diameter (3

Variables	Frequency	Percent	
Sex			
Male	41	36.4	
Female	69	63.6	
Level of asthma control based on GINA* guideline	Frequency	Percent	Mean age ± SD
Controlled	16	14.5	40 ± 16
Partly controlled	26	23.6	35 ± 14
Uncontrolled	68	61.8	32 ± 14
Associated allergic diseases Allergic Rhinitis Allergic conjunctivitis Atopic dermatitis	99 91 41 27	90 82.7 37.3 24.5	
GINA: Global Initiative for Asthma			

Table 1: Baseline characteristics of the study subjects and asthma control level.

SPT	Asthma Control				P value
	Controlled	Partly controlled	Uncontrolled	Total (%)	
Negative SPT	5 (5.1%)	8 (8.2%)	9 (9.2%)	22 (22.4%)	0.038
Positive SPT	9 (9.2%)	13 (13.3%)	54 (55.1%)	76 (77.6%)	
Mean No. of positive inhalant allergens	2.9 ± 3.5	2.2 ± 2.5	3.3 ± 2.9	3.0 ± 2.9	
Total	14 (14.3%)	21 (21.4%)	63 (64.3%)	98 (100%)	
SPT: Skin Prick Test					

Table 2: SPT results according to asthma control level.

± 3 mm); cat epithelia 35 cases (33.7%), mean wheal diameter (2.18 ± 3.44 mm); and German cockroach 23 cases (22.1%), mean wheal diameter (1.15 ± 2.15 mm). However sensitization to other inhalants was variable with low prevalence of molds and outdoor pollens (Table 3). Sensitization to two or more inhalant allergens were common in more than 66% of asthmatics. Among sensitized asthmatics, 38.1% were concomitantly sensitized to *Dermatophagoides pteronyssinus* and *Dermatophagoides farinae*. Sensitization to one or more inhalant allergens was common, particularly to one, two and five different allergens (Table 4).

Dermatophagoides pteronyssinus and Dermatophagoides farinae were the most prevalent inhalant allergens in uncontrolled asthmatics (35.7% and 31.6% respectively), followed by cat epithelia (22.4%), cockroach (14.3%), and dog epithelia (10.2) (Table 5).

The relation between the asthma control and the degree of sensitization to common inhalant allergens is shown in (Figure 1).

Discussion

International guidelines recommend allergy testing in asthmatics to assess sensitization to inhaled allergens. The national asthma education and prevention program-expert panel report (NAEPP-EPR) recommends allergy testing for inhaled allergens in patients who require daily asthma medications [17]. Moreover, the criteria for diagnosis of allergic asthma, particularly in children who have frequent wheezing episodes depends on the presence of atopic characteristics (allergic sensitization to ≥ 1 inhalant allergen, parental history of asthma or personal history of physician diagnosed eczema) [18,19]. Hence, we designed the current study so as to explore the inhalant allergen sensitization status of asthmatics among the Saudi population, which is an approach in congruence with current clinical practice guidelines. The fact that this study is an early research attempt of its kind among the Saudi population; singularizes the study in the repertoire of previous scientific evidence.

This study revealed the predominance of uncontrolled asthma which was consistent with the results of a previous clinical evidence among the Saudi population [5]. This study also revealed that the "allergic phenotype" was predominant in 78% of asthmatics. The spectrum of sensitization to inhalant allergens in patients with allergic asthma in Jeddah was predominated by HDMs followed by cat epithelia and German cockroach. Similar findings were reported by previous studies conducted in the Riyadh region and the eastern province of Saudi Arabia with a high level of inhalant allergen sensitization with varying rates of allergen sensitization [20,21]. In this context, it is also noteworthy that the prevalence of allergic asthma in a UK birth cohort at the age of 4 years was 44%. Sensitization to inhalant allergens was common in this study; HDMs followed by grass pollen and cat were the most common positive allergens [22,23]. Also of note in this regard in China, over 50% of patients with allergic asthma had sensitizations to HDMs.

The most common inhalant allergens causing sensitization among asthmatics in this study were the Dermatophagoides mites. This finding is in congruence with similar results from previous studies from Saudi Arabia and south east Asian countries [15,24].

This pattern of sensitization to HDMs is likely to occur in coastal cities like Jeddah with a humid weather [25]. Worldwide, HDMs are the most common inhalant allergens associated with asthma [26]. Cookson et al. found that the risk for BHR increased significantly in subjects sensitized to HDMs and molds; however subjects sensitized to grass did not demonstrate an increased risk [27]. In a study conducted among children in New Zealand, Sears et al demonstrated that HDM sensitization significantly exceeded other inhalant allergens [28].

In this study, subjects sensitized to HDMs suffered from

Allergen	No. of Patients	Percent	Wheal Diameter (mm)	Mean ± SD
D. pteronyssinus	57	54.8	3-12	3.49 ± 3.53
D. farinae	49	47.1	3-16	3 ± 3
Cat hair	35	33.7	3-13	2.18 ± 3.44
Cockroach G	23	22.1	3-10	1.15 ± 2.15
Salsola kali	4	3.8	3-5	0.16 ± 0.76
Aspergillus mix	7	6.7	3-7	0 ± 1
Blomia tropicalis	12	11.5	3-12	0.59 ± 1.75
Storage mites	14	13.5	3-6	0.67 ± 1.49
Dog epithelium	16	15.4	3-8	0.76 ± 1.74
Timothy grass	8	7.7	3-6	0.38 ± 1.25
Bermuda grass	11	10.6	3-10	0.63 ± 1.76
Rye grass	6	5.8	3-9	0.37 ± 1.28
Mugwort	7	6.7	3-7	0.38 ± 1.35
Plantain	3	2.9	3-5	0.12 ± 0.65
Chenopodium	0	0	<3	0.04 ± 0.28
Date palm	6	5.8	3-8	0.32 ± 1.22
Mesquite	4	3.8	3-6	0.21 ± 0.87
Candida	8	7.7	3-7	0.34 ± 1.12
Cladospoium	8	7.7	3-5	0.35 ± 1.21
Alternaria alt.	8	7.7	3-9	0.38 ± 1.4
Aspergillus	7	6.7	3-7	0 ± 1
Penicillium	1	1	3-7	0.12 ± 0.76
fusarium	1	1	3-6	0.13 ± 0.70
Horse hair	14	13.5	3-20	0.63 ± 2.25
Feather mix	10	9.6	3-5	0.38 ± 1.13
Amaranthus R.	2	1.9	3-7	0.13 ± 0.79
Oleaceae	1	1	3-3	0.05 ± 0.35

Table 3: Prevalence of positive skin reactivity to inhalant allergens and corresponding wheal size.

No. of Allergens	No. of Patients	Percent
1	12	11.5
2	23	22.1
3	10	9.6
4	9	8.7
5	12	11.5
6	3	2.9
7	4	3.8
8	4	3.8
9	2	1.9
14	2	1.9
Total	81	77.9

Table 4: Co-sensitization and polysensitization in study subjects.

Prevalence of inhalant allergens by order	Asthma Control		
	Controlled	Partly controlled	Uncontrolled
1	D.P 8 (8.2%)	D.P 10 (10.2%)	D.P 35 (35.7%)
2	Cat 7 (7.1%)	D.F 8 (8.2%)	D.F 31 (31.6%)
3	D.F 5 (5.1%)	Cat 6 (6.1%)	Cat 22 (22.4%)
4	Dog 4 (4.1%)	Cockroach 4 (4.1%)	Cockroach 14 (14.3%)
5	Horse 4 (4.1%)	Horse 3 (3.1%)	Dog 10 (10.2%)

DP: *Dermatophagoides pteronyssinus;* DF: *Dermatophagoides farinae*

Table 5: Commonest inhalant allergens correlated to asthma control.

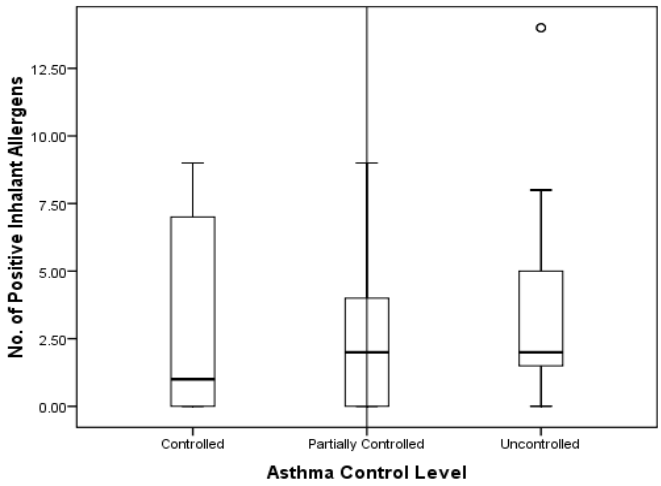

Figure 1: Number of positive inhalant allergens yielding sensitization plotted against asthma control level.

uncontrolled and partly controlled asthma as compared to better control seen among those sensitized to other inhaled allergens (Table 5). This finding is consistent with other studies which demonstrated clear positive relationship between HDM sensitization and airway hyper-responsiveness, poor asthma control and related morbidity in asthmatics [29-31]. This is perhaps attributable to the fact that both sensitization to HDM and poor asthma control are higher in people who are exposed to high levels of HDM allergens. Increased exposure to HDM allergens has been linked to a parallel increase in sensitization in susceptible persons [32,33].

Furthermore in this study, more than 66% of the subjects showed polysensitization towards two or more allergens. This is consistent with the results put forth in a study conducted by Vanessa et al. which revealed a significant correlation between inhalant allergens polysensitization and uncontrolled asthma [34]. In consistency with the results of previous studies, this study too reported co-sensitization with D. pteronyssinus and D. Farinae; this was observed in 38.1% asthmatics [35]. Possible explanations for co-sensitization include parallel sensitization or cross reacting antigens. Specific IgE antibodies to Dp1 and Df1, Dp2 and Df2 as well as Dp10 and Df10 allergens are known to cross react to a great extent [23].

In the current study, sensitization towards the following allergens was seen to a lesser extent as compared to HDMs: cat 33.7% and cockroach 22.1%; with variable but low prevalence of molds and outdoor pollens. This is perhaps because of Jeddah's geographical features wherein arboricultural land is limited and animal exposure is less. Exposure and sensitization to indoor inhalant allergens was found significantly greater in uncontrolled asthmatics compared to subjects with controlled asthma [32].

The results of this study have important clinical implications. In patients with uncontrolled asthma, in whom the identification and removal of specific allergens is being considered, *in-vivo* allergy testing shows great clinical promise and can guide patient management decisions. Allergy testing should be performed at the outset in order to accurately diagnose the case, design therapy and for efficient patient monitoring and lifestyle changes.

However, the study had its own limitations as well. The small size of the study sample is perhaps not adequately representative of the whole lot of asthmatics in Jeddah. As the study was conducted at the allergy clinic at KAUH, most patients included were uncontrolled asthmatics. This is because most cases of controlled or partly controlled asthma perhaps do not visit an allergy specialist. Hence, the nature of the study sample might have got more tilted towards uncontrolled asthmatics; on account of the chosen study site. Hence patients coming to clinic with other allergic diseases and having controlled asthma were also included in the study. The prevalence of sensitization in the asthmatic population in Jeddah is most likely lower and this selection bias might have affected the study result and should be factored in while evaluating the robustness of this study in totality. The study did not assess the exposure to inhalant allergens in sensitized subjects and its correlation with the level of asthma control. In addition, the use and adherence to controller treatment was not assessed which may have an impact on study results.

The author recommends that the health care system should implement a patient workup policy to identify sensitization to common inhalant allergens, early in the course of the disease for newly diagnosed asthmatics; particularly among those with a personal and family history of atopy, and in patients with uncontrolled asthma [10]. This diagnostic workup can include screening allergy tests for common inhalant allergens. Such policy can optimize disease control and reduce morbidity and progression of allergic disease. It can facilitate early implementation of appropriate interventional strategy to avoid inhalant allergens, other lifestyle modifications, guide patient management decisions and monitor patients more effectively.

Therefore, such simple diagnostic measures like allergy testing are instrumental adjuncts for enhancing the clinical evaluation of asthma. This approach shall aid better disease control and less morbidity. Ultimately, this will reduce the burden and cost on health care facilities. However, we recommend that large, more robust, multi-centric and randomized studies be conducted to elucidate the clinical advantages and benefits of these tests. We believe that these issues are imperative for better asthma control and should be addressed essentially in asthma management guidelines.

Conclusion

Asthmatics who are sensitized to one or more inhalant allergens are linked to poor asthma control. Optimal asthma management mandates earlier identification of; associated sensitization to common inhalant allergens and comorbidity; at the outset of the disease. Consequently, allergy diagnostic tools may have management implications for better asthma control.

Author's Contributions

MQ the corresponding author, carried out the cross sectional study, and made substantial contributions to design, methodology, acquisition of data, analysis and interpretation of data; and drafted the

manuscript and revised it critically for important intellectual content. EK participated in acquisition of data, analysis and interpretation of data; research supervision; and helped to draft and critically revised the manuscript. MT participated in acquisition of data and helped to draft and critically revised the manuscript. All authors read and approved the final manuscript.

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