

Dermatophagoides in childhood asthma

Allergy to dermatophagoides associates more severe childhood asthma with a potential role for acaricides

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ABSTRACT

الأهداف: تقييم مدى تأثير عثة الفراش (ديرماتوفوجيد ترينسونس وديرماتوفوجيد فاريني) على الأطفال الذين يعانون من حساسية الصدر، بالإضافة إلى تقييم مدى أهمية استخدام أحد المبيدات الحشرية والطرق الوقائية الأخرى القاتلة لعثة الفراش في السيطرة أو التقليل من شدة هذا المرض.

الطريقة: أجريت هذه الدراسة العشوائية في عيادة أمراض الحساسية لدى الأطفال، مستشفى النور، فرع خليفة، أبوظبي، الإمارات العربية المتحدة وذلك خلال الفترة من سبتمبر 2008م إلى يونيو 2010م. شملت الدراسة 82 طفلاً مصاباً بحساسية الصدر حيث تم تقييم مدى حدة وتأزم المرض لديهم وذلك بناءً على توجيهات المبادرة الدولية لأمراض حساسية الصدر. ولقد قمنا باستخدام اختبار وخزعة الجلد من أجل الفحص عن عثة الفراش (ديرماتوفوجيد ترينسونس وديرماتوفوجيد فاريني)، ومن أجل تمييز المرضى الذين كان لديهم حساسية من أحد نوعي عثة الفراش. ولقد قمنا بتقييم القيمة العلاجية لعثة الفراش من خلال تقدير مدى حدة حساسية الصدر قبل وبعد استخدام المبيدات الحشرية.

النتائج: أظهرت الدراسة وجود العلاقة القوية بين حدوث التحسس لعثة الفراش وحساسية الصدر بصورة شديدة ومستمرة، وأن 81.7% من هؤلاء الأطفال لديهم حساسية لواحدة أو اثنتين من هذه الحشرة. ووجد أيضاً أن استخدام هذا المبيد الحشري يعمل على تحسين أو التقليل من أعراض المرض في صورته الحادة فقط ولكنه ليس له تأثير على التقليل من أعراض المرض في صورته الطفيفة ($p=0.029$). ولقد كان هناك علاقة خطية بين مدى استجابة الأطفال للمبيدات الحشرية وزيادة شدة حساسية الصدر.

خاتمة: أوصت الدراسة في النهاية أهمية اختبار الحساسية بالوخز الجلدي كجزء من الفحص الروتيني لأي مريض يعاني من حساسية الصدر، وأن يخضع هؤلاء الذين لديهم حساسية لهذه الحشرات بالذات إلى بعض الإجراءات الوقائية والعلاجية الخاصة مثل استخدام المبيدات الحشرية للفراش للقضاء على هذه الحشرات وبالتالي التقليل أو السيطرة على أعراض هذا المرض خاصة في الحالات المزمنة أو الشديدة.

Objectives: To evaluate hypersensitivity to *Dermatophagoides pteronyssinus* (*D. pteronyssinus*) and *Dermatophagoides farinae* (*D. farinae*) in pediatric patients with asthma, and the use of acaricides.

Methods: This is a randomized controlled trial in 82 asthmatic children. They were recruited and evaluated for severity and chronicity according to the Global Initiative for Asthma Guidelines. The study was carried out in the Pediatric Allergy Clinic, Al Noor Hospital, Khalifa Branch, Abu Dhabi, United Arab Emirates between September 2008 and June 2010. Skin prick test (SPT) was performed including *D. pteronyssinus* and *D. farinae*, and for those who were sensitive to one, or the other. The therapeutic value of acaricides was evaluated by assessing the severity of asthma before and after their use.

Results: Approximately 81.7% of asthmatics were sensitive to house dust mites (HDM). Hypersensitivity was associated with the more severe and persistent asthma ($p=0.029$). The manifested severity of asthma was not HDM species-specific. There was a linear association between response of children to acaricides and increasing severity of asthma.

Conclusion: Hypersensitivity to HDM is an important factor for persistent and severe forms of asthma. Acaricides can help control childhood asthma, and we recommend SPT as part of the routine work-up of patients with asthma to determine HDM sensitive patients that can benefit from acaricides use.

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Asthma is the most common chronic disease in childhood.¹ Approximately 80% of asthmatic children have an allergic component, and high levels of allergen exposure have been linked to increased asthma symptoms.² House dust mites (HDM) are considered as major indoor allergens, to which infants and children can be exposed to levels sufficient to cause sensitization and exacerbation of their allergies.³⁻⁵ These microscopic arthropods primarily infest fabrics, feed on human skin scales, and their debris is the major source of allergens in house dust.⁶ Water supply in the air, seasonal changes in relative humidity can affect the concentrations of HDM allergen contributing to allergic symptoms in the sensitized children. Higher concentrations of HDM allergens are usually found in older homes and in warm humid regions.^{7,8} As the Arabian Gulf region is situated in a warm and humid area, the indoor climatic conditions are favorable for mites and molds. Allergic reactions to these allergens were found in clinical studies conducted in this region.⁹ With the commercial availability extracts of different allergens for cutaneous hypersensitivity testing (including that for HDM), skin prick test (SPT) has been included in the diagnostic criteria of asthma and other allergic conditions.¹⁰ Specific immunotherapy against HDM sensitization that is based on SPT can be effective in atopic diseases including asthma, resulting in reduction of specific immunoglobulin (Ig)E levels against HDM allergens with concomitant increases in the serum levels of the Th1 cytokines, interferon-gamma (IFN- γ) and the tolerogenic cytokine interleukin (IL)-10.¹¹⁻¹⁴ Neem oil spoils the basic mite food and manipulates hormones responsible for mite growth and reproduction resulting in a lethal anti-HDM action. Combining acaricides with vacuum cleaning at bedrooms can reduce HDM count and patient exposure to these allergens.¹⁵ The objective of this study was to evaluate the occurrence of HDM hypersensitivity as seen by hypersensitivity to *Dermatophagoides pteronyssinus* (*D. pteronyssinus*) and *Dermatophagoides farinae* (*D. farinae*) in pediatric patients with asthma, and to assess the value of using Neem oil extract with other environmental anti-HDM measures as a therapeutic tool for asthma among children.

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Methods. The research was carried out in accordance with the Declaration of Helsinki considered as a cornerstone for ethics in human research.¹⁶ This study is a randomized controlled trial in 82 children with bronchial asthma including 49 males and 33 females. Their age ranged from 6-12 years with mean age of 8.9 ± 1.4 years, patients were chosen by a simple random way from the Pediatric Allergy Clinic, Al Noor Hospital, Khalifa Branch, Abu Dhabi, United Arab Emirates during the period between September 2008 and June 2010. Ninety-five patients were enrolled in the study, 9 patients did not continue the study as they changed their living place and did not attend for follow up and 4 patients were non-compliant to the use of acaricide/anti HDM measures as per protocol.

An ethical approval was obtained prior to the study and consent has been taken from parents of our studied patients and/or patients. The diagnosis of asthma and the classification of its severity were carried out according to Global Initiative for Asthma (GINA) Guidelines 2004.¹⁷

Inclusion and exclusion criteria. We have included children who are established and well known asthmatic children as diagnosed by history of recurrent chest wheezing, nocturnal cough, chest tightness, and dyspnea, positive SPT and a decreased forced expiratory volume in one second, (FEV1) by spirometry or peak expiratory flow meter. We excluded children with other chronic chest diseases, patients who have received antihistamines within a week prior to SPT and children with history of anaphylaxis. Patients were subjected to full history taking: including symptoms of asthma, recurrence, severity, nocturnal symptoms, and type of medications used, past or family history of atopy together with a complete physical examination focusing on manifestations of asthma either the patient in acute attack or controlled at time of examination as well as other forms of atopy.

Skin prick test. The test was carried out by a trained nurse under the consultants' supervision. Using a disposable plastic 1mm needle to puncture through the drop of allergen extract put on the flexor surface of forearm by a standardized dropper. The use of a standardized dropper helps to avoid the variation in the reaction size based on the amount of the allergen in the drop that can be affected by the size of the drop. The result was read after 20 minutes, it was considered positive if the induration reaction to the allergen was 3mm above the diameter of the control induration reaction. All patients were skin tested for control and for histamine as the standard positive, saline as the

standard negative together with 18 allergens including *D. farinae*, *D. pteronyssinus* and the most common foods, epithelia, moulds and pollens. Patients were instructed to discontinue antihistamine therapy one week before their appointment to avoid the suppressive effects of antihistamines on skin test results. Skin prick test solutions were supplied from Stallergenes, Cedex, France and were stored in a refrigerator at 2-8°.

The use of acaricides (Neem oil extract). Neem oil extract preparation was used as a therapeutic tool for patients with sensitivity to one or both strains of HDM as proven by SPT, parents were instructed to use it for the patient's vacuumed mattresses, pillows, and blankets. Regarding environmental anti-HDM measures, instructions were given to parents for removing carpets and curtains from the bedrooms, avoidance of stuffed toys, and hot washing of all bedding once/week.¹⁸ Patients continued their prescribed treatment as needed and they were educated regarding the manifestations and the therapeutic measures for asthma including proper use of relievers as salbutamol by inhalation according to GINA guidelines.¹⁷

A follow up visit was arranged after 4 weeks for assessment of asthma symptoms. Good response has been defined as improvement of symptoms from persistent to intermittent asthma and from more severe to milder form of the disease while poor response was related to lack of improvement or moving to a more severe degree.

Statistical analysis. Statistical analysis was carried out by using SPSS-PC statistical software program, version 11 (SPSS, Inc., Chicago, IL, USA). Groups were compared by analysis of variance and the difference between or among groups were tested using exact tests such as Fisher's exact test or linear-by-linear association considering p value of less than 0.05 as significant value. Pearson correlation coefficient were computed to assess the associations between the size of SPT and severity of asthma. A p-value <0.05 was considered statistically significant.¹⁹

Results. Of 82 patients with childhood asthma, (age ranged from 6-12 years and the mean age of the group was 8.9 ± 1.4 years), 49 patients (59.8%) were males and 33 patients (40.2%) were females. Seventy patients (85.4%) were Arabs and 12 patients (14.6%) were non-Arabs (Table 1). Table 1 also shows the classification of asthmatic patients according to GINA 2004. Thirty-three patients (40.2%) were classified with mild intermittent asthma, 26 patients (31.7%) with mild persistent asthma, 15 patients (18.3%) with moderate persistent asthma while only 8 patients (9.8%) suffered severe persistent asthma.

As shown in Table 2, among children who had mild intermittent asthma, 66.7% were hypersensitive to HDM compared to 92.3% of children with mild persistent asthma. As well as 93.3% of those who had moderate persistent asthma and 87.5% of children classified as severe persistent asthma have been found to be HDM hypersensitive. Table 2 also shows that there is a significant difference between asthmatic children who are HDM hypersensitive to HDM compared to those otherwise ($p < 0.042$). Those asthmatic children who manifested hypersensitivity to HDM represented 81.7% of the total children studied.

Moreover, linear by linear association of the severity of asthma among HDM sensitive children have shown

Table 1 - Characteristics of asthmatic children under study.

Character	N	(%)
Gender		
Male	49	(59.8)
Female	33	(40.2)
Nationalities		
Arabs	70	(85.4)
Non Arabs	12	(14.6)
Asthma severity		
Mild intermittent	33	(40.2)
Mild persistent	26	(31.7)
Moderate persistent	15	(18.3)
Severe persistent	8	(9.8)

Table 2 - The distribution of the house dust mite (HDM) among asthmatic children of different degrees of severity.

Exposure	Severity of asthma				Total	
	Mild intermittent	Mild persistent	Moderate persistent	Severe persistent		
	n (%)	n (%)	n (%)	n (%)	n	(%)
HDM(+)	22 (66.7)	24 (92.3)	14 (93.3)	7 (87.5)	67	(81.7)
HDM(-)	11 (33.3)	2 (7.7)	1 (6.7)	1 (12.5)	15	(18.3)
Fisher's exact test value=7.425, $p=0.042$ (significant, 2-sided), Linear-by-linear association=4.82, $p=0.029$ (significant)						

Table 3 - Hypersensitivity of patients with intermittent and persistent asthma to either *Dermatophagoides pteronyssinus* (*D. pteronyssinus*) or *Dermatophagoides farinae* (*D. farinae*) or to both strains of house dust mite (HDM) studied.

Causative agent of hypersensitivity	Two-level asthma severity	
	Mild intermittent (HDM+)	Persistent (HDM+)
	n (%)	n (%)
<i>D. pteronyssinus</i>	0 (0)	3 (100)
<i>D. farinae</i>	1 (100)	0 (0)
Double agents of hypersensitivity (<i>D. pteronyssinus</i> + <i>D. farinae</i>)	21 (33.3)	42 (66.7)
Fisher's exact test =2.88, p=0.20 (not significant, 2-sided)		

Table 4 - Response to anti house dust mite (HDM) measures (including Neem oil extract and environmental anti-HDM measures) among HDM sensitive patients with different asthma severities.

Severity of asthma	Response to anti-HDM measures		OR 95% confidence interval
	Poor response	Good response	
Mild persistent	14 (58.3)	10 (41.7)	5.58 (4.1-7.4)
Moderate persistent	4 (28.6)	10 (71.4)	3.1 (2.3-4.9)
Severe persistent	1 (14.3)	6 (85.7)	2.2 (1.5-2.9)
Linear-by-linear association=5.53, p=0.024 (significant, 2-sided). Data are express as number and percentage (%). OR - odds ratio			

that there is a significant difference in the proportion of HDM hypersensitivity among different severity groups ($p<0.029$, odds ratio of 1.89 with 95% confidence interval of 1.21-3.17). Hypersensitivity to HDM is most likely to affect the patients with persistent and more severe degrees of asthma, rather than patients with mild intermittent asthma.

Looking at mild intermittent asthmatics who were sensitive to HDM (22 patients) it was found that 18/22 patients (81.2%) were sensitive to *D. pteronyssinus* and 19/22 patients (86.4%) were sensitive to *D. farinae*, while patients with persistent asthma who were sensitive to HDM (45 patients) the hypersensitivity to *D. pteronyssinus* was 43 and *D. farinae* was 40 patients representing 95.6% positivity for *D. pteronyssinus* and 88.9% positivity for *D. farinae*.

Table 3 shows that asthma severity is not affected by hypersensitivity to a single strain of HDM (either *D. pteronyssinus* or *D. farinae*) or to both strains (both

D. pteronyssinus and *D. farinae*) ($p>0.05$) and that the severity of asthma was not HDM species-specific.

Table 4 shows that there is a linear association between the response of children to anti-HDM measures including the use of Neem oil extract and other described environmental measures across increasing severity of asthma ($p=0.024$), odds ratio 3.47, 95% confidence interval 2.31-5.16). Patients with more severe degrees of asthma showed better response than those with milder degrees. Our study revealed that there is a significant correlation ($r=0.16$, $p=0.013$) between more severe degrees of persistent asthma, and the size of SPT hypersensitivity reaction to HDM (whether to *D. pteronyssinus* and *D. farinae*, or both). This indicates that there is low association ($r=0.16$) between the size of the SPT and the increasing severity of asthma.

Discussion. The Arabian Gulf region is among the areas with high prevalence of atopy in the world.^{20,21} Its desert nature, with the hot, humid weather predisposes to indoor living in an air-conditioned environment. Prevalence rates of asthma range between 15-30%.²¹⁻²⁵

Among our asthmatic patients, the prevalence of the sensitization to HDM was high (81.7%), this goes in line with authors highlighting HDM (with mesquite, grass and pollens) to constitute major sensitizing allergens in UAE in particular and in the Arabian Gulf Region in general followed by indoor allergens, such as animal dander and moulds.^{26,27} Several authors have described clinical improvement when mite elimination and avoidance strategies were employed.^{20,28} Again, this rate of sensitization is supported by the idea that HDM are among the major environmental aeroallergens to which asthmatic and other atopic patients are hypersensitive as stated in the official list of allergens maintained and updated by the Allergen Nomenclature Committee.^{29,30} High rates of positivity for HDM specific IgE antibodies including Der p 1, Der p 2 Der f 1 and Der f 2 were found among asthmatic patients by different researchers.³¹

A study has been conducted to asthmatic children in Bahrain studying the prevalence of sensitization to aeroallergens and foods. A total of 95 asthmatic children were enrolled and categorized as follows: 71.6% mild, 20% moderate, and 8.4% severe asthma. This is almost similar to the distribution of patients across the range of asthma severity reported in our study. Overall, 67.4% of children were atopic; 56.8% were sensitive to inhalant allergens including HDM and 39% were sensitive to foods. House dust mites hypersensitivity here is less than that found in our patients, a difference that can be explained by differences in genetic constitution and

in the living conditions between the studied groups. The atopic profile was generally similar to asthmatic children in the region and worldwide.³² Another study carried out in UAE have mentioned HDM among the most common sensitizing allergens in the population with a prevalence of 9.5%, such a difference from our work can be explained by different methodology and by the difference in study population as it was carried out in adults, and has included patients who are suspected to have allergic nature of their diseases compared to our studied group with confirmed allergic nature.²⁷ In previous studies, we conducted on patients with allergic rhinitis and atopic dermatitis in the same locality, we found that 76-74.5% of our studied patients were sensitive to HDM.^{9,20} This shows the importance of HDM as a common among patients with asthma and even with other atopic diseases as well.

Our patients with hypersensitivity to HDM were found more likely to suffer from a more persistent and more severe form of asthma as shown in Table 2. Similarly, atopic patients with HDM hypersensitivity in the same age group and locality were found to suffer more severe and more chronic forms of allergic rhinitis and atopic dermatitis as well. The early and long term exposure to HDM allergens may be responsible for such higher severity and persistence of atopic diseases associating HDM hypersensitivity.^{9,20}

Our study has shown as well that patients with higher degree of hypersensitivity to HDM as shown by a larger SPT reaction do suffer more severe disease. The use of a standardized dropper in the SPT helped us to avoid the possibility of having false size of the SPT reaction caused by variation of allergen. Extract drop size as there is a dose dependent reaction size known to happen with skin tests.³³ The importance of the size of the reaction in the diagnosis of atopy to be correlated with the degree of hypersensitivity and with the severity of clinical signs was agreed by other authors.³⁴

Our work has shown a significantly improvements among patients with more severe degrees of asthma after using neem oil extract, this is supported by the findings of Van der Heide et al³⁵ who has reported a decline in HDM number and improvement of airway hyper reactivity following acaricide treatment. However, another group has mentioned that current chemical and physical methods aimed at reducing exposure to allergens from HDM seem to be ineffective and cannot be recommended as prophylactic treatment for asthma patients sensitive to mites.³⁶ Notably, neem oil extract was not mention in the study.

The significant improvement that has occurred among patients with severe asthma but not with

those with mild disease can be explained by the nature of constant exposure to HDM and its link to the more severe and persistent degrees of asthma so that the elimination of HDM allergens can result in the improvement of such patients suffering severe asthma. Also, this can be explained by the fact that some atopic patients including asthmatics do suffer HDM hypersensitivity among many other allergens, so even control on HDM exposure cannot produce a constant improvement among patients of all classes of the disease due to exposure to other several implicated allergens.^{34,37,38}

Study limitations. The study limitation of this study include the possibility that hypersensitivity to other allergens (other than HDM) might have interfered with the persistence and severity of asthma and might have modified the response to acaricides.

In conclusion, hypersensitivity to *D. pteronyssinus* and *D. farinae* appears as an important risk factor not only for asthma, but for asthmatic children developing more severe and more persistent degrees as well. Anti HDM measures including the use of neem oil extract as an acaricide and environmental anti HDM measures can help controlling asthma among HDM sensitive patients especially those with the more severe and persistent degrees.

We recommend SPT to be carried out as a part of the routine work up of patients with asthma so that those who are sensitive to HDM can undergo special measures helping to control their disease. We also recommend assessing the response to anti HDM measures among patients with asthma who are solely HDM sensitive. The response of patients who are exclusively hypersensitive to HDM to acaricides can be a point for future research, also, the inadequate response among some asthmatics motivates us for further studies focusing on more effective interventions among such patients.

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