Clinical features of children with mosquito allergy

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Abstract

Background: The aim of this study was to document the clinical features of children with mosquito allergy and investigate the possible associations between demographic features and type of reactions in this population. Methods: Children with large local or unusual reactions after mosquito bites who attended to our outpatient pediatric allergy department were enrolled in the study along with control subjects. Results: A total of 180 children (94 with mosquito allergy and 86 age and sex-matched control subjects) with a median age of 6.8 years (IQR 5.5-9.3) were enrolled. Atopy (35.1% vs. 11.6%, p<0.001) and grass pollen sensitization (28.7% vs. 8.1%, p<0.001) were significantly more frequent in children with mosquito allergy. Skin prick test with mosquito allergen was positive in only 6 children (6,4%). Grass pollen sensitization was most common in children (28.7%) followed by sensitization to house dust mite (9.6%). 30 children (31.9%) had an accompanying atopic disease such as allergic rhinitis, asthma or atopic dermatitis. Bullae were significantly more frequent in children with asthma (41.7% vs.15.9, p=0.034). The median duration of symptoms after onset were significantly longer in patients with ecchymosis, with immediate wheals and in children whose symptoms start in 20 min to 4 hours after mosquito bites. Conclusions: The role of commercially available tests in the diagnosis of children with mosquito allergy is limited. There is an association between unusual, large local or exaggerated reactions after mosquito bites and allergic diseases in children. The severity of reactions increases with age and particularly in children with atopic background

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Running Title: Mosquito allergy in children

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ABSTRACT

Background: The aim of this study was to document the clinical features of children with mosquito allergy and investigate the possible associations between demographic features and type of reactions in this population.

Methods: Children with large local or unusual reactions after mosquito bites who attended to our outpatient pediatric allergy department were enrolled in the study along with control subjects.

Results: A total of 180 children (94 with mosquito allergy and 86 age and sex-matched control subjects) with a median age of 6.8 years (IQR 5.5-9.3) were enrolled. Atopy (35.1% vs. 11.6%, p<0.001) and grass pollen sensitization (28.7% vs. 8.1%, p<0.001) were significantly more frequent in children with mosquito allergy. Skin prick test with mosquito allergen was positive in only 6 children (6,4%). Grass pollen sensitization was most common in children (28.7%) followed by sensitization to house dust mite (9.6%). 30 children (31.9%) had an accompanying atopic disease such as allergic rhinitis, asthma or atopic dermatitis. Bullae were significantly more frequent in children with asthma (41.7% vs.15.9, p=0.034). The median duration of symptoms after onset were significantly longer in patients with ecchymosis, with immediate wheals and in children whose symptoms start in 20 min to 4 hours after mosquito bites.

Conclusions: Our results indicate that the role of commercially available tests in the diagnosis of children with mosquito allergy is limited. There is an association between unusual, large local or exaggerated reactions after mosquito bites and allergic diseases in children. The severity of reactions increases with age and particularly in children with atopic background.

Keywords: children, large local reaction, mosquito allergy, large local reaction, unusual reaction

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INTRODUCTION

Mosquito bites cause typical local cutaneous reactions in children and adults. Although these reactions decrease quality of patients, the symptoms resolve in several days without any systemic or severe symptoms in the majority of the population (1). However, there are patients who encounter unusual or "exaggerated" reactions such as large local, atypical or systemic reactions after mosquito bites. Even if the immune mechanisms associated with the reaction type and severity are not yet completely found out, these patients are defined as mosquito allergic patients and due to the limited availability of the in vivo and in vitro diagnostic methods, the diagnosis is primarily made with the help of clinical history and physical examination findings (2).

Several cross-sectional and longitudinal studies are performed in order to determine the natural course of the disease. It has been suggested that natural desensitization may occur in adolescence and young children may be at increased risk of having severe reactions to mosquito bites (3, 4). However, the data regarding the demographic features of children with mosquito allergy is limited.

The aim of this study was to document the characteristics of children with mosquito allergy and investigate the possible associations between demographic features and clinical reactions in this population.

METHODS

Study design, setting and participants

Children aged 2 to 17 who had admitted to the Pediatric Allergy and Asthma Unit of Gulhane School of Medicine with reactions after mosquito bites between 2015 and 2018 were enrolled in the study along with age and sex-matched control subjects who tolerated several mosquito bites without any unusual or large local reaction. Children in the control group had no history of physician-diagnosed allergic diseases and they admitted to our outpatient department for routine medical checkup.

Mosquito allergy was defined as large local reactions to mosquito bites consist of itchy, red, warm swellings appearing within minutes of the bites, and atypical reactions such as itchy papules, ecchymotic, vesiculated, blistering, bullous reactions, appearing in 6 hours after the bites and persisting for days or weeks (5). Demographic data, history of mosquito allergy (onset of the reaction, reaction type) and personal and familial history of other atopic diseases were recorded. Physical examination, morphology and other clinical manifestations of skin lesions were recorded. The skin reaction features of the children at the time of enrollment were classified into five stages due to the lifetime course of the process of sensitization and desensitization, as previously reported: stage 1, the bites cause no or little reaction (wheal $<$ 4 mm, erythema $<$ 4 mm or papule $<$ 3 mm); stage 2, delayed reaction only (erythematous papules of $>$ 4 mm develop 3–4 h after bite and with a peak at 24–36 h); stage 3, immediate reaction followed by delayed reaction (wheal of $>$ 4 mm develops a peak [?] 20 min after bite); stage 4, immediate reaction only; and stage 5, those with repeated bites eventually lose the reactions (2).

Asthma was defined as current symptoms (wheeze and cough) and positive bronchodilator responsiveness (improvement of FEV_1 by 12% or more following administration of 200 mcg salbutamol), and/or a positive response to a trial of therapy with inhaled or oral corticosteroids (6). Allergic rhinitis was defined by the presence of rhinitis symptoms (rhinorrhea, nasal obstruction, nasal itching and sneezing), which are reversible spontaneously or with treatment in children with aeroallergen sensitization in the skin-prick test (7). Atopic dermatitis was defined as the presence of pruritus and a relapsing eczematous rash typically found over flexor surfaces (8).

The study was approved by the institutional review board of Gulhane School of Medicine and written informed consent was obtained from parents.

Study measurements

Skin tests

All children underwent skin prick testing (SPT) to mosquito with commercial extract of *Aedes communis* (Stallergenes, Anthony, France), along with common aeroallergens for our region (9), including house-dust mites (*Dermatophagoides pteronyssinus* and*Dermatophagoides farinae*), grass pollen mix (Phleum pratense, Poa pratensis, Dactylis glomerata, Lolium perenne, Festuca pratensis, and Avena eliator) weed pollen mix (Artemisia, Urtica, Taraxacum, Plantago) tree pollen mix (Alnus glutinosa, Corylus avellane, Populus alba, Ulmus minor, Betula alba) molds (Alternaria, Cladosporium, Penicillium, and Aspergillus) and animal dander (cat and dog). Histamine (10 mg/ml of histamine phosphate) and 0.9% saline were used as positive and negative controls, respectively. Weal 3 mm greater than negative control was considered a positive reaction.

Blood eosinophil counts and serum total IgE levels

Blood eosinophil counts were determined from Coulter Counter (Beckman Coulter, Fullerton, CA, USA) leucocyte measurements. Total serum IgE level was measured using ImmunoCAP (Phadia AB, Uppsala, Sweden).

Statistical Analysis

Analyses were performed using SPSS Statistics v21.0 (IBM, Chicago, IL, USA). Not-normally distributed continuous data were expressed as median and interquartile ranges (IQR). Group comparisons were carried out using Mann–Whitney U-test or ANOVA as appropriate for the continuous, and the chi-square test or Fisher test for categorical variables. The correlation coefficients between clinical manifestations and other clinical variables were determined using Spearman's rank correlation or Pearsons coefficient. A P level <0.05 was considered significant.

RESULTS

Descriptive statistics

A total of 180 children (94 with mosquito allergy and 86 healthy controls) with a median age of 6.8 years (IQR 5.5-9.3) were enrolled. Characteristics of the study groups are presented in Table 1. There were no significant differences between the children with mosquito allergy and healthy controls in terms of age, sex, and skin prick test positivity to mosquito allergen. Atopy (35.1% vs. 11.6%, p<0.001) and grass pollen sensitization (28.7% vs. 8.1%, p<0.001) were significantly more frequent in children with mosquito allergy and they had significantly higher eosinophil counts and total IgE levels compared to healthy controls.

Clinical features of children with mosquito allergy

Clinical characteristics of the children with mosquito allergy are presented in Table 2. The median age of onset of reactions to mosquito bites was 3.3 years (IQR 2.0-5.6). The median duration of symptoms after onset was 2.7 years (IQR 1.2-4.3). 11 children (11.7%) had a positive family history of mosquito allergy. Skin prick test with mosquito allergen was positive in only 6 children (6,4%) with mosquito allergy. 35.1% of patients had sensitization to at least one aeroallergen. Grass pollen sensitization was most common in children (28.7%) followed by sensitization to house dust mite (9.6%). 30 children (31.9%) had an accompanying atopic disease such as allergic rhinitis, asthma or atopic dermatitis. 4 children (4.3%) had symptoms of Skeeter Syndrome with large cellulitis-like local inflammatory reaction and fever.

Clinical manifestations of children with mosquito allergy

Table 3 shows the clinical manifestations of the patients and the comparison of symptom duration according to the features of the reactions. Most children in our study were in Stage 2 (72.8%) followed by children in Stage 3 (26.1). There was only one child (1.1%) in Stage 4. There were no children in Stage 1 or Stage 5. The most common skin lesion was erythematous papule (92.6%). Generalized urticaria was detected only in 4.3% of the children. In the 76.1% of children, the skin reactions developed later than 4 hours after mosquito bite. The lesions recovered within 7 days in two third of the children (61.7%). The diameter of the lesions was larger than 10 cm in 9.4% of the children. Ecchymosis was significantly more frequent in children with reactions larger than 10 cm compared to children with smaller lesions (47.1 vs 17.3, p=0.021) and in boys compared to girls (32.0% vs.13.6, p=0.036). Bullae were significantly more frequent in children with asthma (41.7% vs.15.9, p=0.034).

Correlation between the characteristics of symptoms and clinical features

There were no significant correlations between age, age at onset of symptoms, gender, duration of symptoms, time to recovery of the lesions, stage of the bite reaction and skin test positivity to mosquito. The median duration of symptoms after onset were significantly longer in patients with ecchymosis [3.8 years (IQR 2.4-4.8) vs. 2.4 years (IQR 0.8-3.8); p=0.024], immediate wheals [3.8 years (IQR 2.5-5.1) vs. 2.5 years (IQR 0.9-4.1); p=0.047]. The median duration of symptoms was also significantly longer in children whose symptoms start in 20 min to 4 hours when compared to children by whom the symptoms develop later than 4 hours after mosquito bites [3.5 years (IQR 1.6-4.6) vs. 2.0 years (IQR 0.7-3.7); p=0.027]. There were no significant correlations between skin test positivity to mosquito and clinical features.

DISCUSSION

The results of our cross-sectional study, which conducted in a group of children with mosquito allergy, revealed the high frequency of aeroallergen sensitization along with atopic diseases in the study population. The diagnostic role of the mosquito commercial extract was very limited in children. Our results also found out several associations between the duration of symptoms and the features of skin reactions after mosquito bites in children with mosquito allergy.

One third of the children had at least one allergic disease such as allergic rhinitis, asthma or atopic dermatitis. When we tried to compare our findings with previous studies, we have noticed a lack of studies that were performed by children with mosquito allergy. The study of Manuyakorn et al.(10) is the only previous childhood study that presents the demographic and clinical features of children with mosquito allergy. They have reported data from 50 Thai children and although they did not perform skin prick tests with aeroallergens, the frequency of accompanying atopic diseases was 76% in children with mosquito allergy. However, the details and the definitions of the atopic diseases were not described. In the study of Kulthanan et al.(11) which reported the clinical features of 70 adults with mosquito allergy, 58.6% of the patients had a personal history of atopy. Similar to our results, nearly half of the patients had allergic rhinitis. Due to the design of our study, we have included only healthy children without any physician-diagnosed allergic disease in the control group. Therefore, a clear statement regarding the increased prevalence of allergic rhinitis in children with mosquito allergy cannot be extracted from our results. Nevertheless, the prevalence of physician-diagnosed allergic rhinitis in children varies between 8.1%-13.4% according to the results of previous childhood studies in Turkey (12, 13). In consequence with the previous studies, it can be speculated that large local reactions and/or unusual reactions after mosquito bites are more encountered in patients with allergic diseases. Further studies including children with allergic diseases and without reactions after mosquito bites are needed to support this hypothesis.

The prevalence of atopy and particularly grass pollen allergy were significantly more frequent in our cohort of children with mosquito allergy when compared to healthy children without any unusual reaction after mosquito bites. We have found a positive relationship between grass pollen allergy and mosquito reactivity in skin prick tests.

In the study of Kulthanan et al. house dust mite was the most common allergen in skin prick tests in patients with mosquito allergy (11). Scala et al. (14) have performed a multicenter study in 205 individuals reporting large local reactions after mosquito bites and found significant relationships in SPT reactivity between mosquito (*Aedes communis)* and house dust mite (*D.pteronyssinus*), cockroach (*B. germanica*), bee (*Apis mellifera*) allergens. They have concluded that in individuals with severe local reactions following mosquito bites, the immune response to mosquito allergens is associated with both species-specific and cross-reactive bee venom components, suggesting the a "bee-mosquito syndrome." In our cohort, there was no child with bee or wasp allergy. Nevertheless, only 32 children (34%) had a history of bee and/or wasp sting.

Bemanian et al. have investigated the prevalence of insect aeroallergens in their cohort of 86 patients (31 children and 55 adults) with allergic rhinitis (15). Approximately one third of the patients were sensitized to mosquito allergen in skin prick test. However, there are no data about the reactions after mosquito bites. Cantillo et al.(16) have evaluated the cross-reactivity between mosquito allergens (*Aedes aegypti*) and other arthropods in serum samples of 34 patients with asthma and/or allergic rhinitis and reported a cross-reactivity between Aedes aegypti and mites, shrimp and cockroach.

Arias-Cruz et al. (17) have aimed to identify the prevalence of mosquito allergy and performed skin prick tests with a common mosquito species in Mexico (Aedes aeigypti) in 482 patients ranged in age from 2 to 58 years. Mosquito prick test was positive in 3 of 12 patients (25%) with large local reactions and no significant difference were found between patients with or without mosquito allergy. In the childhood study of Manuyakorn et al., 34% of the children were positive to skin prick test with Culex pipenes, whereas 32% of the children had positive specific IgE against *Aedes communis* . In adults with mosquito allergy the reported prevalences of positive skin prick tests and positive IgE antibodies to various mosquito species are higher compared to children and vary between 46.8-80 % and 45.8-73.8%, respectively (11, 14). The prevalence of skin prick test positivity to mosquito allergen was 6.4% in our cohort and there was no difference when

compared to control group. The sensitivity and specificity of currently available tests in patients with a history of exaggerated or unusual responses to mosquito bites are reported to be limited (2).

Various researchers have investigated the natural course of reactions after mosquito bites and classified the patients in 5 stages (18, 19). Delayed reactions are frequent in children whereas the prevalence of immediate reactions reported to increase with age during adolescence (20, 21). In parallel with the previous findings, the majority of the children in our cohort were in stage 2 and 3 (10, 11). Moreover, we found out that the children who develop wheals in a short time after mosquito bites had longer history of symptoms. Erythematous papules were the most frequent lesions in our group. Another interesting finding of our study is the significantly higher prevalence of bullous reactions in children with asthma (41.7% vs.15.9, p=0.034). Bullous reactions to mosquito bites have been previously reported (22, 23), however there is no observed association with an atopic background so far. The exact pathogenesis of the reactions are unknown, however a hypersensitivity reaction against salivary antigens emerges as a plausible explanation (24). Severe skin reactions with various systemic symptoms are encountered in patients with certain conditions such as Epstein-Barr virus (EBV) associated lymphoproliferative diseases and natural killer (NK) cell lymphoproliferative disorders. We have consulted the children in our cohort with our pediatric hematology department and none of the children in the study group had an underlying hematologic disease during our follow-up period. Mosquito bites must be kept in mind in the differential diagnosis of children with bullous reactions and particularly with asthma.

We did not perform specific IgE testing in our patients, nevertheless performing these in vivo or in vitro tests especially in young children may have little benefit. On the other hand, it was performed in a center which was specialized for children with allergic diseases. The diagnostic procedures and the longitudinal follow-up of the patients were made by pediatric allergy specialists. Our study is one of the few childhood studies that provide unique data about children with unusual or exaggerated reactions after mosquito bites. Its prospective and controlled design along with a fairly large number of participants are other superiorities.

In conclusion, our results indicate that the role of commercially available tests in the diagnosis of children with mosquito allergy is limited. There is an association between unusual, large local or exaggerated reactions after mosquito bites and allergic diseases in children. The severity of reactions increases with age and particularly in children with atopic background.

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Table 1. Demographic and laboratory characteristics of the study groups (n=180)

	Mosquito Allergy (n=94)	**Healthy Controls (n=86)**	**p**
Age, years	6.6 (4.4-9.7)	6.9 (6.1-8.7)	0.36

Male sex	53.2	46.5	0.37
SPT positivity to Mosquito	6.4	1.2	0.12
Atopy	35.1	11.6	**< 0.001**
- Grass pollens	28.7	8.1	**< 0.001**
- House dust mites	9.6	4.7	0.20
- Cat dander	2.1	0	0.50
- Mold	5.3	1.2	0.21
- Dog dander	0	0	NA
- Tree pollens	2.1	1.2	0.61
- Weed pollens	1.1	1.2	0.95
Eosinophils, %	2.9 (1.6-4.3)	1.8 (1.3-2.5)	**0.001**
Eosinophils, (/ml)	195 (140-300)	135 (80-200)	**< 0.001**
Total IgE (IU/ml)	62 (22-153)	19 (8-69)	**< 0.001**
Data are presented as percentage or median (interquartile range)	Data are presented as percentage or median (interquartile range)	Data are presented as percentage or median (interquartile range)	Data are presented as percentage or median (interquartile range)

Table 2. Clinical characteristics of the children with mosquito allergy (n=94)

Age, years	6.6 (4.4-9.7)
Male sex	53.2
Age at symptoms start, years	3.3 (2.0-5.6)
Duration of symptoms after onset, years	2.7 (1.2-4.3)
Family history of mosquito allergy	11.7
Family history of allergic diseases	25.1
Accompanying allergic diseases	31.9
- Allergic rhinitis	22.3
- Asthma	12.8
- Atopic dermatitis	5.3
Skeeter Syndrome	4.3
Data are presented as percentage or median (interquartile range)	Data are presented as percentage or median (interquarti

Table 3. Clinical manifestations of the children with mosquito allergy (n=94)

Features of skin lesions		**Duration of symptoms (years)**	**p**
Stage of Reaction			
- Stage 1	0		0.39
- Stage 2	72.8	2.5 (0.9-4.3)	
- Stage 3	26.1	3.2 (1.3-4.5)	
- Stage 4	1.1	3.5 (3.5-3.5)	
- Stage 5	0		
- *Erythematous papule*			0.22
Yes	92.6	2.8 (1.2-4.6)	
No	7.4	2.0 (1.1-2.9)	
- *Vesicle*			0.25
Yes	43.6	3.0 (1.6-4.5)	
No	56.4	2.4 (0.9-4.2)	
- *Ecchymosis*			**0.024**

Yes	23.4	3.8 (2.4-4.8)	
No	76.6	2.4 (0.8-3.8)	
- Immediate wheal			**0.047**
Yes	16.3	3.8 (2.5-5.1)	
No	83.7	2.5 (0.9-4.1)	
- Bullae			0.29
Yes	19.1	2.5 (0.6-4.0)	
No	81.9	2.8 (1.2-4.6)	
- Generalized urticaria			0.65
Yes	4.3	3.5 (1.8-3.9)	
No	95.7	2.6 (1.1-4.5)	
Onset of reaction after bite			**0.027**
- 20 min – 4 hr	23.9	3.5 (1.6-4.6)	
- > 4 hr	76.1	2.0 (0.7-3.7)	
Time of resolving			0.68
- 1-6 days	61.7	2.5 (1.2-4.1)	
- > 7 days	38.3	2.8 (1.1-4.7)	
Data are presented as percentage or median (interquartile range)	Data are presented as percentage or median (interquartile range)	Data are presented as percentage or median (interquartile range)	