

Mosquito Allergy in Children: Clinical features and limitation of commercially-available diagnostic tests

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Abstract

Objective: To determine the clinical features of mosquito allergy in children and the ability of commercially available mosquito allergy tests to detect children with mosquito allergy in Thailand.

Methods: Patients with mosquito allergy aged 1 month to 18 years were recruited. Demographic data, history of mosquito allergy (onset of the reaction, reaction type) and clinical features were recorded. A skin prick test using a commercially available whole body allergen extract from *Culex pipiens* was performed, and serum was tested for specific IgE antibodies to *Aedes communis* whole body extract.

Results: A total of 50 patients with mosquito allergy were enrolled. The median age of enrolled children was 6.2 years with an average age of onset of 2 years [interquartile range (IQR) 1–6]. Half of the children were female. The most common skin lesion from mosquito allergy was erythematous papules ($n = 45$, 76.3%). The majority of children (58%) were in stage 3 (immediate and delayed type of reactions). One child (2%) was in the desensitization stage after 4.6 years of symptoms. The causative mosquito species could be identified only in 26 (52%) children: 16 (32%) children were positive for *Aedes communis*, 17 (34%) children were positive for *Culex pipiens* and 7 (14%) children were positive for both *Aedes communis* and *Culex pipiens*. Having positive IgE antibodies against *Aedes communis* was significantly more common in boys ($n = 13$, 48.1%) than girls ($n = 3$, 13%) ($p < 0.01$).

Conclusion: Immediate and delayed skin reaction is the most common manifestation in mosquito allergy children. Commercially available tests for mosquito allergy can detect only 30–50% of children with mosquito allergy.

Keywords: mosquito, allergy, children, skin test, specific IgE, immediate reaction, delayed reaction

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Introduction

Allergic reactions to mosquito bites are common, and may decrease quality of life.¹ Severe local reactions such as urticarial rash or systemic reactions including generalized urticaria and anaphylaxis have been reported.² *Culex quinquefasciatus*, *Aedes aegypti*, *Aedes albopictus* and *Anopheles minimus* are the four most important mosquito species in the Southeast Asia region including Thailand.³ Mosquito allergy can be diagnosed by clinical symptoms after a witnessed bite by a mosquito. Investigations including skin test or specific IgE antibodies to mosquito allergens help in confirming the diagnosis in children

with skin lesions but no witnessed mosquito bite. However, different regions of the world have different types of local mosquitoes. Commercially available mosquito allergy tests were developed from mosquitoes not commonly found in Southeast Asia and their sensitivity in detecting mosquito allergy in children is unknown. This study aimed to determine the clinical features of mosquito allergy in children and the ability of the commercially available mosquito allergy tests to detect children with mosquito allergy in Thailand.

Methods

A cross-sectional study was performed at the Department of Pediatrics, Faculty of Medicine, Ramathibodi Hospital, Mahidol University, Bangkok, Thailand from January 2012 to September 2014. Children with a history of reaction after mosquito bite, aged 1 month to 18 years, were enrolled. The diagnosis of mosquito allergy was defined by bite reactions (immediate wheals and flares with a peak within 20 min and delayed reaction manifested as itchy indurated erythematous papules with a peak at 24–36 h and then gradually resolving within days or weeks.^{4,5} Other reactions include vesicles, bullae, ecchymosis, generalized urticaria and angioedema). Demographic data, history of mosquito allergy (onset of the reaction, reaction type) and personal and familial history of other atopic diseases were recorded. Clinical manifestations of skin lesions were recorded. The skin reaction patterns of the patients at the time of the study 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 minimal or no reaction (wheal < 4 mm, erythema < 4 mm or papule < 3 mm); stage 2, delayed type of reaction (erythematous papules of > 4 mm develop 3–4 h after bite and with a peak at 24–36 h); stage 3, both delayed and immediate type of reaction (wheal of > 4 mm develops a peak ≤ 20 min after bite); stage 4, only immediate wheals; and stage 5, those with repeated bites eventually lose the reactions.⁶

A skin prick test (SPT) was performed with whole body *Culex pipiens* extract (ALK-Abelló, Hørsholm, Denmark), positive control (histamine 10 mg/ml) and negative control (0.9% NaCl) using Duotip-Test® (Lincoln Diagnostics, Dallas, TX, USA). The results were read at 15 min. A positive result yielded a wheal at least 3 mm in diameter larger than the negative control. Sera were tested for specific IgE antibodies to *Aedes communis* whole body extract (CAP-System, Thermo Fisher Scientific, Waltham, MA, USA). This study was reviewed and approved by the human rights and ethics committee of the Faculty of Medicine, Ramathibodi Hospital, Mahidol University, Thailand. All of the participants were subject to an informed consent about the objective of the study.

Statistical analysis

Descriptive statistics (e.g. median, minimum, maximum and percentages) were used to describe demographic data and the positivity of SPT and specific IgE to mosquitoes. All statistical data analyses were performed using the SPSS 17.0 software package.

Results

Fifty children with mosquito allergy were enrolled. Twenty-seven children (54%) were male. The median age was 6.2 years [interquartile range (IQR) 3.1–8.5]. Thirty-eight children (76%) had a personal history of atopic diseases.

Clinical manifestation and clinical course of mosquito allergy

The median age at onset of developing mosquito allergy was 2 years (IQR 1–6). The median duration of symptoms after onset was 2.29 years (IQR 0.54–4.75). The most common primary skin lesion was erythematous papules ($n = 45$, 76.3%). Twenty-seven children (54%) developed skin lesions less than 20 min after mosquito bite. The skin lesions were healed within 1–3 days in 46% of children. Thirty-two children (72.7%) developed a secondary skin lesion. The most common area of involvement was the leg (85.7%). Fifty-eight percent of children were in stage 3 of mosquito bite reaction. One child (2%) was in the desensitization stage after 4.6 years of symptoms (Table 1).

Comparing preschool (less than 5 years) vs. school age (5–10 years) and adolescent children (more than 10 years), there were significant differences in the median age of onset of developing mosquito allergy: 0.58 years (IQR 0.25–1) vs. 2.71 years (IQR 0.38–4.96) vs. 3.83 years (IQR 1–7.92), respectively ($p < 0.001$, Table 1). The median duration of symptoms after onset was also significantly different among groups: 1.17 years (IQR 0.42–3.04) vs. 2.71 years (IQR 0.38–4.96) vs. 3.83 years (IQR 1–7.92), respectively ($p < 0.001$). However, there were no significant differences in clinical manifestations including stage of disease, primary and secondary lesions, onset of skin reaction after mosquito bite and time of resolution after mosquito bite among groups (Table 1).

Comparing children with different stages of disease, there were no significant differences in the median age at onset and median duration of symptoms after onset (Table 2).

Causative mosquito allergen and clinical features of mosquito allergy

The causative mosquito species could be identified only in 26 (52%) children: 16 (32%) children were positive for *Aedes communis*, 17 (34%) children were positive for *Culex pipiens* and 7 (14%) children were positive for both *Aedes communis* and *Culex pipiens* (Table 3). No significant difference in the positivity of the test was observed among age groups (Table 3). Comparing children who had positive and negative tests for mosquito allergy, secondary skin lesion followed by mosquito bite reaction was significantly associated with the result of the test for *Culex pipiens* ($p = 0.04$). Fifteen (88.2%) mosquito allergy children with a positive test for *Culex pipiens* had a secondary skin lesion while 60.6% of children who did not have secondary lesions had a positive test for *Culex pipiens*. Post-inflammatory hyperpigmentation was demonstrated in 14 children (77.8%) with a positive test for *Culex pipiens*, whereas it was demonstrated in 18 children (69.2%) with a negative test for *Culex pipiens*. The result for IgE antibodies against *Aedes communis* was significantly associated with sex ($p < 0.01$): 48% of boys had a positive test for *Culex pipiens* but only 13% of girls had a positive test for *Culex pipiens*. There was no significant association between atopic history of patients, atopic history of familial members, characteristics of primary skin lesions, stage of mosquito allergy reaction and onset/time of resolution of skin lesion between patients who had positive and negative mosquito allergy testing (by SPT or specific IgE antibodies) (Table 4).

Table 1. Clinical manifestation of mosquito allergy children

	Overall N=50	Age group			p value
		Age <5 yr N=17	>5-10yr N=22	> 10 yr N=11	
Age at onset (year): median(IQR*)	2 (1-6)	0.58 (0.25-1)	3.5 (2-6)	7 (3-10)	<0.001
Duration of symptoms after onset (year): median(IQR*)	2.29 (0.54-4.75)	1.17 (0.42-3.04)	2.71 (0.38-4.96)	3.83 (1-7.92)	0.005
Sex: male, n(%)	27(54)	7 (41.2)	11(50)	9(81.8)	0.1
Stage of Mosquito bite reaction, n(%)					0.5
• Stage 1	7(14)	4(23.5)	3(13.6)	0(0)	
• Stage 2	11(22)	2(11.8)	5(22.7)	4(36.4)	
• Stage 3	29(58)	11(64.7)	12(54.5)	6(54.5)	
• Stage 4	2(4)	0(0)	1(4.5)	1(9.1)	
• Stage 5	1(2)	0(0)	1(4.5)	0(0)	
Primary lesion, n(%)					
• Erythematous papule	45(76.3)	17(100)	19(86.4)	9(81.8)	0.55
• Immediated wheal	6(10.1)	1(5.9)	4(18.2)	1(9.1)	0.24
• Vesicle/Bullae	6(10.1)	4(23.5)	1(4.5)	1(9.1)	0.87
Secondary lesion, n(%)					
• Post-inflammatory hyperpigmentation	32(72.7)	12(70.6)	14(63.6)	6(54.5)	0.57
• Secondary bacterial infection	2(4.5)	1(5.9)	1(4.5)	0(0)	1
• Atrophic scar	8(18.1)	2(11.8)	3(13.6)	3(27.3)	0.61
• Prurigo nodularis	2(4.5)	1(5.9)	1(4.5)	0(0)	1
Onset of skin reaction (after mosquito bite), n(%)					
• <20 min	27 (54)	9(52.9)	11(50)	7(63.6)	0.94
• 20 min – 1 hr	17 (34)	5(29.4)	8(36.4)	4(36.4)	
• 1 – 4 hr	4 (8)	2(11.8)	2(9.1)	0(0)	
• > 4 hr	2 (4)	1(5.9)	1(4.5)	0(0)	
Time of resolving, n(%)					
• < 1 day	11(22)	4(23.5)	4(18.2)	3(27.3)	0.06
• 1-3 days	23(46)	5(29.4)	13(59.1)	5(45.5)	
• 3- 7 days	11(22)	7(41.2)	4(18.2)	0(0)	
• > 7 days	5(10)	1(5.9)	1(4.5)	3(27.3)	

*IQR, the interquartile range

Table 2. Comparison between the age of patients at the time of study, duration of symptoms after onset and the stage of bite reaction

Stage of bite reaction	Number of patients (%) N=50	Median age of patients at the time of study; year (IQR*)	Median duration of symptoms after onset; year (IQR*)
1	7(14)	4.25 (2.08-6.17)	2.17(0.08-3.25)
2	11 (22)	6.42 (5.75-11.75)	0.42 (0.08-3.33)
3	29 (58)	6.83 (2.04-8.67)	2 (0.75-5.62)
4	2 (4)	8.83 (6.75-10.92)	6.33(4.75-7.92)
5	1 (2)	5.58 (-)	4.58 (-)

*IQR, the interquartile range

Table 3. Comparison of the result of skin prick test for *Culex pipiens* and specific IgE to *Aedes communitis* among age group

	Overall N=50	Age group			p value
		Age <5 yr N=17	>5-10yr N=22	> 10 yr N=11	
Test positive for either <i>Culex pipiens</i> or <i>Aedes communitis</i> , (%)	26(52)	7(41.2)	12(54.4)	7(63.6)	0.49
Skin prick test positive to <i>Culex pipenes</i> , n(%)	17(34)	4(23.5)	9(40.9)	4(36.4)	0.52
IgE positive to <i>Aedes communitis</i> , n(%)	16(32)	3(17.6)	9(40.9)	4(36.4)	0.29

Table 4. Comparison of baseline characteristic and clinical manifestation between mosquito allergy patients who had positive and negative tests

Mosquito allergy clinical symptoms	SPT for <i>Culex pipiens</i>		p-value	Specific IgE for <i>Aedes communitis</i>		p-value
	positive (n=17)	negative (n=33)		positive (n=16)	negative (n=34)	
Age (months): median(IQR)	7 (1.3-15.8)	6.1 (0.5-10.1)	0.96	6.9 (3-15.8)	5.8 (0.5-12.9)	0.56
Sex, n(%)						
• Male	8(29.6)	19(70.4)	0.48	13(48.1)	14(51.9)	< 0.01
• Female	9(39.1)	14(60.9)		3(13)	20(87)	
Atopic disease, n(%)						
• Yes	13(34.2)	25(65.8)	1.00	14(36.8)	2(16.7)	0.29
• None atopic disease	4(33.3)	8(66.7)		24(63.2)	10(83.3)	
Familial history of atopy, n(%)						
• Yes	11(39.3)	17(60.7)	0.37	11(39.3)	5(22.7)	0.21
• No	6(27.3)	16(72.7)		17(60.7)	17(73.3)	
Age onset (months): median(IQR)	4 (0.1-12)	2 (0.2-10)	0.57	3 (0.3-10)	2 (0.1-12)	0.69
Primary lesion, n(%)						
• Erythematous papule	15(83.3)	30(73.2)	1.00	14(87.5)	31(72.1)	0.65
• Immediated wheal	2(11.1)	4(9.8)	1.00	1(6.3)	5(11.6)	0.65
• Vesicle/Bullae	1(5.56)	5(12.2)	0.65	0(0)	6(14.0)	0.15
Stage of Mosquito bite reaction, n(%)						
• Stage 1	2(11.8)	5(15.2)	0.68	2(11.8)	5(15.2)	0.16
• Stage 2	5(29.4)	6(18.2)		5(29.4)	6(64.7)	
• Stage 3	10(58.8)	19(57.6)		7(43.8)	22(64.7)	
• Stage 4	0(0)	2(6.1)		2(12.5)	0(0)	
• Stage 5	0(0)	1(3.0)		0(0)	1(2.9)	
Secondary lesion, n(%)						
• Post-inflammatory hyperpigmentation	14(77.8)	18(69.2)	0.05	10(66.7)	22(75.9)	0.88
• Secondary bacterial infection	1(5.6)	1(3.8)	1.00	0(0)	2(6.9)	1.00
• Atrophic scar	2(11.1)	6(23.1)	1.00	4(26.7)	4(13.8)	0.24
• Prurigo nodularis	1(5.6)	1(3.8)	1.00	1(6.7)	1(3.4)	0.54
Onset of skin reaction after mosquito bite, n(%)						
• <20 min	6(35.3)	21(63.6)	0.11	10(62.5)	17(50.0)	0.54
• 20 min – 1hr	9(52.9)	8(24.2)		4(25.0)	13(38.2)	
• 1 – 4 hr	2(11.8)	2(6.1)		2(12.5)	2(5.9)	
• > 4 hr	0(0)	2(6.1)		0(0)	2(5.9)	
Time of resolving, n(%)						
• < 1 day	3(17.6)	8(24.2)	0.60	4(25.0)	7(20.6)	0.62
• 1-3 days	8(47.1)	15(45.5)		9(56.3)	14(41.2)	
• 3- 7 days	3(17.6)	8(24.2)		2(12.5)	9(26.5)	
• > 7 days	3(17.6)	2(6.1)		1(6.3)	4(11.8)	

Discussion

Mosquito allergy is common in children. However, there are scarce studies reporting on the clinical characteristics of mosquito allergy in children. Mosquito bite reactions in humans are known to change from stage 1 to stage 5. We have demonstrated that the majority of mosquito allergy children were in stage 3 and no children aged less than 5 years were in stage 4 or 5. In a previous study on the relationship between mosquito allergy stage and age it was demonstrated that no children aged less than 6 years were in stage 4 or 5 and the majority of patients with mosquito allergy were in stage 3.^{6,7} We found that 50% of mosquito allergic children were male. This was in contrast to a recent study in Thai adults which found that 80% of adults with mosquito allergy were female.⁷

This finding may suggest that boys with mosquito allergy may develop desensitization in adulthood more than girls with mosquito allergy. The only child who developed the desensitization stage in our study is also male. However, a longitudinal study on the clinical symptoms of mosquito allergy in children is needed to confirm this observation. Similar to a previous study in Thai adults with mosquito allergy,⁷ the cutaneous reaction after mosquito bite in our study showed erythematous papules as the most common skin reaction.

The mosquito allergy tests currently available in many countries including Thailand were developed from whole body extract proteins. We have demonstrated that only 50% of children with a history of mosquito allergy had a positive test

to these commercial whole body extract mosquito tests: skin test for *Culex pipiens* or specific IgE for *Aedes communis*. If only one test was selected the positivity of the test was decreased to 30%. The pathogenesis of allergic reactions to mosquitoes involves an immunological reaction to mosquito saliva.⁸ Peng et al compared protein content, IgE binding antigens and skin reactivity between commercial and laboratory-made mosquito extracts and found variation in skin reactions to commercial mosquito allergen extracts.⁹ Laboratory-made mosquito allergen extracted from saliva proteins provided an 80% positivity result in a recent study in adult mosquito allergy.⁷ Wang et al have shown that a mosquito saliva capture enzyme-linked immunosorbent assay is more sensitive and specific than a whole body extract-based UniCAP test in the diagnosis of mosquito allergy.¹⁰ The diagnosis of mosquito allergy is obtained from skin reactions caused by hypersensitivity to the bite of mosquitoes. However, similar reactions can occur from the bites of other insects.¹¹ Evidence of IgE sensitization from skin test or specific IgE to specific insects has a role in helping diagnosis and the avoidance of specific insects. In addition, immunotherapy to mosquitoes has been demonstrated to be effective in cases with severe allergic reaction to mosquitoes.¹² As a result, there is a need to develop mosquito allergen extracts prepared from saliva or salivary glands of common mosquitoes in Thailand for the diagnosis and treatment of mosquito allergy especially for immunotherapy for the causative mosquito.

In conclusion: immediate and delayed skin reaction is the most common manifestation in mosquito allergy children. Commercially available tests for mosquito allergy can detect only 30–50% of children with mosquito allergy. A better mosquito allergen extract from salivary proteins is needed for better diagnosis and specific mosquito immunotherapy in mosquito allergy children.

Acknowledgements

This study was supported by a Research Development Grant (grant ID: IO R11057008) from the Faculty of Medicine, Ramathibodi Hospital, Mahidol University, Bangkok, Thailand.

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