

Increased rate and greater severity of allergic reactions to insect sting among schoolchildren with atopic diseases

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The question of whether atopic diseases are a risk factor for allergic reactions to insect sting is still unresolved. The aim of this study was to evaluate the association between atopic diseases (asthma, allergic rhinitis, atopic eczema) and allergic reactions to insect stings among schoolchildren in Israel. A self-report questionnaire of the International Study of Asthma and Allergies in Childhood was administered to a national sample of 13–14-yr-old schoolchildren. Questions regarding reactions to insect stings were added. A total of 10,021 questionnaires were available for analysis. Among the children who reported insect stings (56.3%), the prevalence of current asthma was 6.0%, of allergic rhinitis, 10.5%, and of atopic eczema, 8.7%, with no significant differences from the whole study population. Among children with any of the atopic diseases, 36.9% reported an allergic reaction to insect sting compared to 24.8% of the non-atopic children ($p < 0.0001$). On multivariate analysis, asthma, allergic rhinitis, and atopic eczema were found to be significant risk factors for allergic reactions of any severity. Children in the atopic group had a significantly higher rate of severe allergic reactions than the non-atopic children, and relatively higher rates of milder ones ($p < 0.0001$). Asthmatic patients with severe allergic reactions had more parameters of severe asthma than asthmatic patients with mild or no reactions. In conclusions, allergic diseases are associated with a higher rate and greater severity of allergic reactions to insect sting in children. The severity of the allergic reaction is related to the severity of the asthma symptoms.

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Insect sting is one of the most common causes of anaphylaxis worldwide (1–3). Diagnostic sting challenges have been shown to provide information on the risk of further anaphylactic reaction (4, 5). There are limited and conflicting reports whether atopy is a risk factor for allergic reactions including anaphylaxis to insect stings.

Abbreviations: CI, confidence interval; LLR, large local reaction; MSR, mild systemic reaction; OR, odds ratio; SSR, moderate to severe systemic reaction.

Most of the studies were published in the late 1950s and 1970s and reported no association between clinical insect sting allergy and inhalant allergies (6–8). The presence of an atopic disease (such as allergic rhinitis, asthma, and atopic eczema) apparently did not predispose patients to an allergic reaction to venom (3, 9–12). Findings for this association in high-risk groups such as beekeepers were inconclusive (13, 14).

Studies in children are very limited. One investigation of Italian primary schoolchildren

noted that a positive skin prick test to Hymenoptera venoms was related to a positive skin test to foods or aeroallergens, but there was no association of a positive skin test to venom and clinical allergic parameters, such as current wheezing and rhinoconjunctivitis (15). The association between atopic diseases (mainly asthma) and the severity of the allergic reaction to insect sting is also unclear. One study found that although asthmatic patients had no increased risk of a systemic reaction to Hymenoptera stings, in those who did have a systemic reaction, it was significantly more severe than in non-asthmatic patients (16). Furthermore, in asthmatic patients, symptoms of asthma were more often a main feature of their anaphylactic response (17, 18).

In a previous analysis, we described the prevalence of insect stings and allergic reactions in a large cohort of 13–14-yr-old children in Israel, where the order Hymenoptera is common (19). According to the Israeli Ministry of Environment, four Hymenoptera genera can be found in Israel; honey bee, *Vespula germanica* (yellow jacket), *Polistes dominulus*, and *Vespa orientalis*. Honey bee and yellow jacket account for most of the allergic reactions to insect stings in the country (20). We reported that 56.3% of the children had been stung at least once in their lifetime (19). Of these, 20.5% had a large local reaction (LLR), 11.6% a mild (cutaneous) systemic reaction (MSR), and 4.4% a moderate to severe systemic reaction (SSR). Arab children reported significantly more allergic reactions than Jews and so did children who were stung more than once.

The aim of the present study was to evaluate the prevalence and severity of allergic reactions to insect stings in children with atopy compared with children with no atopy.

Methods

Sampling strategy

The study was conducted as part of the International Study of Asthma and Allergies in Childhood (ISAAC) (21) and included a national sample of 13–14-yr-old schoolchildren in Israel. The sampling strategy was previously reported in detail (19). To obtain a representative sample, 109 schools were chosen at random from a list of all junior high schools by district that was provided by the Ministry of Education. All eighth-grade pupils in each school selected were included in the study. The number of schools selected from each district was weighted by the

total number of eighth graders in that district and the number of children attending each school. As Jews and Arabs generally attend separate schools, sampling was carried out for each population group separately. For technical reasons, we did not include the specialized school system of the ultra-orthodox Jews, who comprise 5% of the Jewish population in Israel.

Procedure

The study was carried out during the last 2 wk of May 2003. The parents of the children in the selected schools received an explanatory letter with a reply slip that served as an informed consent. The parents were asked to return the slip to the school if they did not want their child to participate in the study. Children who were absent from school on the day of the study were asked to complete the questionnaire on a specified day during the following month.

Questionnaire

The standard core questionnaire developed by the ISAAC (21) was used in the present study. We also added an item on current diagnosis of asthma, several items on demographic and social factors, and six items on history of bee and wasp stings and allergic reactions (19). The questionnaire was completed on an anonymous basis in the children's native language (Arabic or Hebrew), in class. The teachers were instructed not to help the children with the responses.

Definitions

Children who answered 'yes' to the question, 'Do you have asthma or spastic bronchitis?' were considered to have asthma. Children who reported having ever had an intermittent itchy rash (eczema) in a typical distribution, lasting approximately 6 months or more, were considered to have atopic eczema. The children were also asked if they currently suffer from allergic rhinitis. Children who reported having asthma or allergic rhinitis or atopic eczema were considered atopic.

Insect sting reactions were categorized as follows: a large local reaction (LLR) was defined as an induration contiguous to the sting site that was estimated to be >5 cm and persisted for more than 2 days; a mild systemic reaction (MSR) was defined as a reaction occurring within 1 h of the sting and consisting of a cutaneous manifestation, such as generalized hives or angioedema (distant from the sting); a moderate to severe systemic reaction (SSR) was defined as a

reaction occurring within 1 h of the sting and consisting of difficulties in breathing, asthma attack, abdominal pain, or loss of consciousness. The children were asked to reply 'yes' or 'no' to each of the reactions described, so all combinations were possible.

Statistical analysis

Statistical analyses were carried out using SAS package 8.2 (SAS Institute Inc., Cary, NC). Chi-square tests were used to determine the statistical significance of differences in the distribution of categorical variables. A multiple logistic regression model was fitted to the data to evaluate the association between the allergic reactions and the various risk factors. A p-value of <0.05 was considered significant.

Results

Response rate

The sampling process yielded a study population of 14,603 children from 109 schools. Twelve of the schools (total 1403 children) refused to take part in the study, leaving a final sample of 13,200 schoolchildren from 97 schools: 8469 Jews and 4731 Arabs. Of these, 11,255 children filled out the questionnaire, for an overall response rate of 82.9%. An additional 1234 questionnaires were later excluded because the responses were incomplete. Thus, the questionnaires of 10,021 children were available for analysis: 5349 females (53.4%) and 4672 males (46.6%); 6449 Jews (66.1%) and 3308 Arabs (33.9%).

Association of atopic diseases and allergic reaction to sting

Of the 10,021 children, 5644 (56.3%) reported ever having been stung in their lifetime. In this subgroup, the prevalence of current asthma was 6.0% (6.8% for the Jewish children and 4.9% for the Arab children); of allergic rhinitis, 10.5% (10.1% for Jews, 10.9% for Arabs); and of atopic eczema, 8.7% (10.7% for Jews, 5.6% for Arabs). These figures were similar to the rates for these conditions in the whole study population.

Among the children with any atopic disease, 36.9% reported ever having had an allergic reaction of any severity, compared to 24.8% of the non-atopic children ($p < 0.0001$).

Among the children who reported an allergic reaction to sting, ($n = 1500$), 25.4% were atopic, and among the children who were stung, but did not have an allergic reaction 15.7% were atopic ($p < 0.0001$).

Table 1. Prevalence of allergic reactions to stings by atopic diseases and other characteristics

	LLR n (%)	MSR n (%)	SSR n (%)
Current asthma			
Yes	105 (30.8)*	72 (21.7)*	53 (15.5)*
No	1019 (19.2)	568 (10.7)	187 (3.5)
Allergic rhinitis			
Yes	153 (27.4)*	105 (18.8)*	66 (11.8)*
No	911 (18.9)	503 (10.5)	158 (3.3)
Atopic eczema			
Yes	152 (31.9)*	101 (21.2)*	48 (10.6)*
No	936 (18.7)	522 (10.4)	183 (3.7)
Gender			
Female	577 (21.5)†	324 (11.3)	109 (3.8)
Male	530 (18.4)	307 (11.5) ns	127 (4.7) ns
Population group			
Arabs	541 (23.6)*	464 (20.2)*	131 (5.7)*
Jews	568 (17.2)	170 (5.2)	104 (3.2)
Area of residence			
Urban	992 (20.7)*	592 (12.4)*	214 (4.5)†
Rural	116 (14.7)	45 (5.7)	22 (2.8)
Number of stings			
>1	703 (22.9)*	446 (14.5)*	160 (5.2)*
1	307 (14.9)	133 (6.5)	54 (2.6)

ns, non significant; LLR, large local reaction; MSR, mild systemic reaction; SSR, moderate to severe systemic reaction.

* <0.001 .

† <0.01 .

Table 1 shows the prevalence of various allergic reactions to stings by atopic diseases and other risk factors that were identified in our previous study (19). Allergic reactions, especially SSR were significantly more common in children with any atopic disease. On multivariate analysis (Table 2), asthma, allergic rhinitis, and atopic eczema were significant risk factors for each allergic reaction (LLR, MSR, SSR), as were population group (Arabs) and number of stings (>1).

Atopic diseases and severity of the allergic reaction

One thousand and five hundred children had allergic reactions to insect sting. Children with any atopic disease were at a significantly higher risk for having SSR rather than LLR or MSR ($p < 0.0001$) (Table 3). For example, the odds ratio for SSR associated with having asthma was 3.64 (95%CI 2.47–5.37). Population group, area of residence, and number of stings (>1) were not found to be risk factors for SSR specifically. Table 4 shows that asthmatic patients who were stung and reported a SSR had significantly more parameters of severe asthma (such as more than 12 exacerbations per year, school absence because of asthma, etc.) than asthmatic patients who had mild reactions or no reactions at all.

Table 2. Adjusted ORs (95% CIs) for LLR, MSR, SSR*

Factor	LLR	p	MSR	p	SSR	p
Current asthma	1.8 (1.4–2.4)	<0.0001	2.1 (1.5–3.0)	<0.0001	3.5 (2.3–5.4)	<0.001
Allergic rhinitis	1.4 (1.1–1.7)	0.008	1.5 (1.1–2.0)	0.009	2.6 (1.8–3.8)	<0.001
Atopic eczema	2.0 (1.5–2.4)	<0.001	2.3 (1.6–3.1)	<0.001	1.8 (1.1–2.8)	0.006
Gender – Female	1.4 (1.2–1.6)	<0.001	–	–	–	–
Arabs	1.3 (1.1–1.5)	0.003	4.8 (3.8–6.0)	<0.001	1.6 (1.2–2.2)	0.006
Area of residence – urban†	1.6 (1.2–2.0)	0.0004	1.1 (0.8–1.7)	0.5	1.0 (0.6–1.7)	0.9
No of stings > 1	1.8 (1.5–2.1)	<0.001	1.5 (1.2–1.9)	0.0004	1.5 (1.0–2.1)	0.04
LLR	–	–	4.7 (3.9–5.8)	<0.0001	5.5 (4.0–7.5)	<0.001

LLR, large local reaction; MSR, mild systemic reaction; SSR, moderate to severe systemic reaction.

*Adjusted for all other factors listed in the table.

†Rural ≤ 2000 population; urban >2000 population.

Table 3. Odds ratios for SSR by atopic diseases and other characteristics among children with allergic reactions

	SSR n (%)	LLR and/or MSR n (%)	OR (95% CI)	p
Current asthma				
Yes	53 (36.8)	91 (63.2)	3.64	<0.0001
No	187 (13.8)	1169 (86.2)	(2.47–5.37)	
Allergic rhinitis				
Yes	66 (32.7)	136 (67.3)	3.27	<0.0001
No	158 (12.9)	1065 (87.1)	(2.30–4.65)	
Eczema ever				
Yes	48 (25.4)	141 (74.6)	2.01	<0.0001
No	183 (14.5)	1081 (85.5)	(1.38–2.98)	
Population group				
Arabs	131 (16.2)	679 (83.8)	1.06	0.7
Jews	104 (15.4)	570 (84.6)	(0.79–1.41)	
Area of residence				
Urban	214 (16.0)	1120 (84.0)	1.08	0.7
Rural	22 (15.0)	125 (85.0)	(0.66–1.80)	
Number of stings				
>1	160 (16.6)	803 (83.4)	1.26	0.2
1	54 (13.7)	341 (86.3)	(0.89–1.78)	

LLR, large local reaction; MSR, mild systemic reaction; SSR, moderate to severe systemic reaction.

Table 4. Parameters of asthma severity by type of reaction among children with asthma who were stung

Parameters of asthma severity	SSR n (%)	*No SSR n (%)	p
More than 12 exacerbations per year	12 (23.1)	33 (11.7)	0.03
Nighttime symptoms once a week or more	18 (34.0)	43 (15.4)	0.001
Severe exacerbation (talking in words)	28 (53.9)	63 (22.3)	<0.001
School absence (more than 1 wk)	14 (26.4)	30 (10.6)	0.001

LLR, large local reaction; MSR, mild systemic reaction; SSR, moderate to severe systemic reaction.

*MSR, LLR or none.

Discussion

Although food allergy is known to be associated with atopic diseases (22, 23), it is generally accepted that atopic background does not pre-

dispose individuals to allergic reactions following insect stings.

The present study focused on the association between atopic diseases and allergic reactions to insect stings in children. We found that children who reported having one or more atopic diseases also reported having significantly more allergic reactions to insect stings than children without atopic diseases, irrespective of other risk factors such as population group and number of stings that we identified in a previous study (19).

The current data on the association of atopic diseases to insect sting allergy are based mainly on studies from the 1950s and 1970s (4–7). A recent investigation in children from Italy, reported a significant association between a positive skin test to venoms and a positive skin test to foods and aeroallergens, but no association with atopic diseases was observed (15). The study did not address the association between allergic reaction to sting and atopic diseases, possibly because of the very low prevalence of systemic reactions (only four children). More recent studies on stings allergy and immunotherapy in children did not address the issue. The association between allergic diseases and allergic reaction to stings observed in the present study contradicts previous studies in adults. This can be because of different methods and definitions used in those studies or because of differences between adults and children in their allergic reactions to sting.

As insect sting allergy is considered an IgE-mediated disorder, atopic patients, who have higher levels of specific IgE antibodies, would be expected to have more allergic reactions to insect sting. However, as the present nationwide anonymous survey did not include blood sampling, we cannot refer to the level of IgE antibodies to venoms. Yet, it is well recognized that the history and diagnostic tests are imperfectly correlated. The dilemma of negative skin tests in patients

with a convincing history, and a reaction on subsequent stinging has been discussed in the literature (24, 25).

In the present study sample, of the children with allergic reactions to insect sting, those who had an atopic disease had significantly more severe reactions (SSR) than those who did not. This finding is in agreement with previous studies (16–18), but disagrees with an earlier one in a small cohort (117 patients) that observed no correlation between severity of the reaction and atopic disposition (26).

The asthmatic children with severe reactions to insect stings (SSR) reported more on parameters indicative of more severe asthma compared to the asthmatic children who had a LLR, MSR, or no allergic reaction to stings. Accordingly, asthmatic patients with peanut sensitivity have been found more likely to develop fatal reactions (27), apparently owing to their exquisite sensitivity to mediators of anaphylaxis. This finding has important clinical implications given that the decision to start immunotherapy takes into account the risk of a severe reaction at the next sting.

The present study was limited by the use of self-reports by children. One of the concerns is that atopic children may have low threshold for reporting any kind of symptoms and increased awareness of allergic reactions, but it is not reported in the literature.

As mentioned, since this was a nationwide anonymous study, we could not validate the findings with physicians. This could have contributed to some overestimation of the prevalence of allergic reactions, as children's reporting of allergic reactions depends on the definitions that are used and their preconceptions of allergic reactions. However, the ISAAC questionnaire is a validated questionnaire used worldwide (21), and earlier studies found that children's self-reports on respiratory symptoms and asthma were valid, that their reports tended to improve with age (28, 29), and school-age children were able to report effectively on their own general health and well-being (30).

In conclusion, the association between atopic diseases and allergic reactions to stings is stronger than previously reported. Atopic background, mainly asthma, is also associated with more severe reactions, which could affect clinical decisions regarding immunotherapy in children. Successful therapies for the prevention of severe systemic reaction will require a better understanding of the genetic and environmental factors that predispose the individual to sting allergy.

Standardized international studies, including skin tests or blood test for specific IgE antibody,

may contribute to a better understanding of this medical issue and help clinicians to set guidelines for prevention and therapy of anaphylactic reaction to insect sting.

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