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A Longitudinal Study of Hymenoptera Stings in Preschool Children

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Abstract

Background: Insect venom is the second most common cause of anaphylaxis outside of medical encounters. Stings cause over 20% of all anaphylactic deaths and 7% of anaphylaxis in children. To date there have been no longitudinal studies of insect sting events or allergy in preschool children.

Methods: A prospective longitudinal nested observational study in the BASELINE Birth Cohort Study (n=2,137). Sting-related questions were asked at 6 and 12months, 2 and 5years. Skin Prick Testing (SPT) was performed at 2 and 5years. SpIgE testing was performed on selected cases at 2years.

Results: Seventy-seven children(6.8%) were stung by the age of 2. Of these, 25 (32.5%) reported adverse reactions (4 systemic). Eleven(0.9%) had positive SPT at 2years (9 bee, 3 wasp, 1 both). 4 stung children had positive SPT. Two (1 stung, 1 never stung) had positive spIgE to a venom-component at 2 years. 268 children (21.9%) were stung by 5years, 144 (52.1%) reporting local reactions, none systemic. Four children (0.4%) had positive SPT at 5years; 1 bee, 3 wasp. Of the 11 SPT-positive children at 2years, none were still positive at 5years.

Conclusion: This is the first longitudinal study of the natural history of hymenoptera stings and allergy in preschool children. Hymenoptera venom allergy is less common in this cohort than in adults. Systemic reactions were not medically documented in this population, in keeping with previous literature. This study confirms the poor correlation of IgE sensitisation to venom with sting allergy and does not support the common parental request to screen children for sting allergy.

Introduction

Insect venom is the second most common cause of anaphylaxis outside of medical environments (1). Hymenoptera stings (bee and wasp species) cause over 20% of all anaphylactic deaths and 7-19% of anaphylaxis in children (2-4). Hymenoptera venom allergy is known to be more common in adults than in children (4, 5) but there are few data on hymenoptera stings in the paediatric population, particularly in the preschool age group. Three cross-sectional studies apply to an older paediatric population and there are no longitudinal studies (6-8).

Reactions to hymenoptera stings range from transient local reactions, due to the envenomation, to systemic reactions such as anaphylaxis. Factors which predispose to a severe reaction include a large number of stings and increasing age (9). Children who live in a rural area and those with asthma are also more likely to have a severe reaction (6). Children are also more likely to be re-stung than adults (10).

Hymenoptera venom allergy is diagnosed by a positive history of a typical reaction, after a typical sting event, supported by allergy-specific immunological testing for immunoglobulin E (IgE) to the suspected venom (11, 12). Asymptomatic sensitisation, the demonstration of positive IgE based testing in either skin prick testing (SPT) or in the measurement of serum levels of allergen-specific IgE *without* a history of an adverse reaction to the sting is common; rates have been reported between 15-40% (13-15). An Italian study found 3.6% of a mid-childhood paediatric cohort to be sensitised regardless of sting history (16). Clinically significant reactions can also occur in the presence of negative IgE-based skin or serological testing.

The aim of this study was to prospectively determine the cumulative incidence of hymenoptera stings in unselected children under the age of five years in an Irish birth cohort and also to provide longitudinal follow-up on sting events and hymenoptera venom allergy in children.

Methods

This is a longitudinal observational study using data from the Cork BASELINE Birth Cohort Study of 2,137 new-born infants. Infants were recruited from 2008-2011 and followed to five years of age. Data collection was completed in 2016. A detailed description of the Cork BASELINE Birth Cohort Study is available from O'Donovan *et al.* (17). Research objectives and measurements in this birth cohort were conducted according to the guidelines laid down in the Declaration of Helsinki and all procedures were approved by the Clinical Research Ethics Committee of the Cork Teaching Hospitals, [ref ECM5(9) 01/07/2008].

Questionnaires were administered by trained researchers, at 6 and 12 months and at 2 and 5 years of age, and skin prick tests (ALK Abello, Berkshire, UK) were performed at the 2 and 5 year visits. SPT was carried out for bee, vespula and 9 other common allergens with histamine used as a positive control. A reaction larger than 3mm was considered to be positive, in the presence of at least a 3mm response to histamine and no response to saline. Among the questions asked at 6 and 12 months and at 2 years was 'Has your child had an adverse reaction to bee or wasp sting in the last six months?' At 2 and 5 years, parents were asked 'Was your child ever stung by a bee or wasp?' and 'Did your child ever have an adverse reaction to a bee or wasp sting?' In a nested cross-sectional study, those who reported a positive sting history at 2 years were contacted by phone with a further questionnaire

relating to the sting history, including whether the child was inside or outside at the time, location of the sting on the body and treatment. Also at 2 years, bloods were taken, with parental consent, for bee and wasp component-resolved spIgE measurements in those with a positive sting history or with a positive SPT to bee or wasp. Test kits were donated by Thermofisher Ireland and tests were performed in the accredited clinical laboratory of Cork University Hospital, according to agreed manufacturer's protocols. Intradermal testing was not performed in this study of asymptomatic infants and children who were being screened for sensitisation based on history and SPT results and we did not have any medically-confirmed systemic reactions to stings.

IBM SPSS v22 ® statistical analysis software (IBM Corp. released 2012 Armonk, NY, USA) was used to perform descriptive and inferential testing. Chi square tests were used to test differences across groups. A p-value of less than 0.05 was considered significant.

Results

Six of 1809 children (0.33%) were parentally reported to have had an adverse reaction to a bee or wasp sting in their first six months, 4 were local only and 2 were reported to be systemic (Table 1), but none were assessed by a doctor or referred to either the BASELINE study team or the paediatric allergy clinic.

At one year, 16/1691 (0.9%) children were parentally reported to have experienced an adverse reaction to a sting. Twelve of these reactions were local and four were reported as systemic, but again no reported systemic reaction was medically confirmed or referred. Two local reactions were medically confirmed.

Parents of 77 (6.8% of 1,209) children reported their child had been stung by a bee or wasp before 2 years, with only a single child stung more than once. 54 (70%) of those previously stung were contacted by phone for further details of the sting. The median age at sting was 19 months and children were more likely to be stung while outdoors (66%). Half of the children were stung on the finger or hand (47%) and almost one-fifth (18%) were stung on the face (see Fig 1). Most did not seek healthcare advice (42%), but where sought, a pharmacist, not a doctor, was most frequently contacted (8%). The most commonly used treatment was vinegar (18%) and 21% did not use any treatment.

SPT were carried out at the 2 year visit. 11 of 1,232 (0.89%) were positive; 9 to bee, 3 to wasp and a single child was SPT positive to both. 4 of the 11 (36%) SPT positive children at 2 years had been stung. Thirty-nine children had spIgE testing at 2 years and only two children were positive (Table 2). One child had not been stung before 2 years and was not stung between 2 and 5 years of age either. This child was SPT positive to bee at 2 years, but had negative sting SPTs at the 5 year visit. This child was spIgE positive for both bee and wasp and was food and aeroallergen sensitised at 2 and 5 years to peanut and dust mite. The second child with a positive spIgE result at 2 years had been stung without incident and had negative SPT at both time-points. He had a positive spIgE to wasp only and was aeroallergen sensitised at 2 and 5 years to dust mite. Children with positive SPT to bee or wasp were found to have a higher rate of sensitisation than the general population (Table 3).

At 5 years, 21.9% (n=268) of children reported a positive sting history. 144 (52.2%) reported local reactions only with no large local reactions or systemic reactions (Table 1). The other 124 children reported no reaction. SPT for bee and wasp were performed in 937 children at five years, 4 (0.4%) of which were positive; one for bee and three for wasp.

Table 4 compares those who were stung with those who were not previously stung by 5 years of age, including SPT results at 2 and 5 years. Boys were slightly more likely to be stung than girls (24.3%, n=153 vs 19.3%, n=115; p=0.024), however there was no difference in reported local reactions between the sexes (54.9% vs 45.1%; p= 0.478).

Three of those who had a positive skin prick test at 2 years were subsequently stung between the 2 and 5 year visits. One of these children experienced a local reaction and the other two children had no reaction.

Repeat SPT was carried out at 5 years. Seven of the nine children with positive SPT to bee at 2 years had a negative result at 5 years and the other two were lost to follow-up. Of the three children who had a positive SPT to wasp at 2 years, one was lost to follow-up and the remaining two had a negative result at 5 years.

Discussion

Previous cross-sectional studies from Ireland, Spain and Israel have examined hymenoptera sting allergy in older children (6-8). We report the first longitudinal study of hymenoptera stings and sting allergy in preschool children. Our research shows the cumulative incidence

of hymenoptera sting events to be 6.8% at 2 years and 21.9% at 5 years. Published data reports figures ranging from 37.5% - 68.9% in school-going children (6-8) with even higher ranges reported in adults (56-94%) (18), which support our findings of increasing incidence over time.

Previous studies of systemic reactions in older children have indicated ranges of 0.5% up to 11% (6-8, 19). The number of systemic reactions reported in our study was low throughout our follow-up to 5 years, only 8 children in total or 2% of those that were stung. It is notable that these were parent-reported events and therefore may be over-estimated as only three cases were diagnosed by a doctor and none was referred to the BASELINE study team, the emergency department or to the paediatric allergy clinic. Yavuz *et al.* reported a rate of systemic reactions as high as 56% when self-reported by children (20).

SPT were positive in 0.9% at 2 years and 0.4% at 5 years, with only one child sensitised to both bee and wasp at 2 years. Five of those who had a positive SPT at two years had not been stung, implying that cross-reactivity from IgE antibodies for different venoms or bites can take place, as reported in previous studies (9). No child was sensitised at both 2 and 5 years, indicating that this non-specific venom sensitisation can wane, and three were subsequently stung, with no systemic reaction. This confirms the low specificity of skin prick testing in a general population. Bilo *et al* reported low numbers of sting-induced anaphylaxis despite a high prevalence of asymptomatic sensitization (21). Our findings are in keeping with previous studies suggesting that SPT should be performed only where clinically indicated by a report of an adverse reaction that is more than local envenomation (11, 12). Component-resolved IgE findings should similarly be interpreted with caution due to the low number of positive results and should be considered for use only in the context of sting history and SPT results.

Limitations of the Study

The most significant limitation was that these events were parent-reported rather than medically diagnosed, leading to likely over-estimation of adverse reactions, which may have been simply local envenomation. This is offset by the low rates of positive SPT and spIgE when used.

Conclusion

Hymenoptera stings are a normal part of childhood, and their frequency predictably increases with age. No systemic reactions were medically confirmed in this study, in keeping with ranges reported in previous literature (6). A positive SPT or spIgE result for venom components neither correlates with a positive sting history nor predicts venom-allergy in those who have not yet been stung. This supports recommendations that venom skin prick testing should not be performed in the general population (12).

This research is the first longitudinal study of hymenoptera venom allergy in a preschool paediatric population and the data should reassure parents and clinicians about the usually benign nature of hymenoptera stings in preschool children.

Table 1. Sting history across infancy and early childhood

	6 months[1] (n=1,809)	**1 year**[1] (n=1,691)	**2 years** (n=1,209)	**5 years** (n=1,226)
Previously stung			77 (6.8)	268 (21.9)
Bee			7 (10.8)[2]	
Wasp			41 (63.1)[2]	
Unsure which			17 (26.1)[2]	
Adverse reactions *(for those previously stung)*	6	16	25 (32.5)	144 (52.2)
Local reaction	4	12	21 (27.3)	144 (52.2)
Systemic reaction[3]	2	4	4 (5.2)	0 (0.0)
Skin prick test positive			11 (0.9)	4 (0.4)
Bees			9 (0.7)	1 (0.1)
Wasps			3 (0.2)	3 (0.3)

*Values shown as N (%) unless otherwise specified.
[1]Only data on adverse reactions collected at 6 & 12 months, no sting history
[2] Data on type of sting only collected at 2 years
[3]None medically confirmed

Table 2. Children with positive spIgE results

	Child 1	Child 2
Sting history		
Stung before 2 years	No	Yes
Stung between 2 to 5 years of age	No	No
Skin Prick Testing		
Bee at 2 years	Positive	Negative
Wasp at 2 years	Negative	Negative
Bee at 5 years	Negative	Negative
Wasp at 5 years	Negative	Negative
Aeroallergen at 2 & 5 years	Dust mite positive	Dust mite positive
Food at 2 & 5 years	Peanut positive	Negative
spIgE results (expressed in KU/L)		
Bee Venom	0.53	<0.1
Wasp Venom	<0.1	<0.1
Bee Phospholipase A2	<0.1	<0.1
Common Wasp Venom	0.14	0.19
Wasp Phospholipase A1	<0.1	<0.1

Table 3. Sensitisation rates

Sensitisation at 2 and 5 years	Any sensitisation	Sensitised to aeroallergen	Sensitised to food
2 years			
Overall rate (n=1442)	10.8 (156)	7.6 (110)	6.2 (89)
Sting SPT positive children at 2 years (n=11)	54.5 (6)	45.5 (5)	45.5 (5)
5 years			
Overall rate (n = 1007)	23.8 (239)	23.5 (236)	4.1 (40)
Sting SPT positive children at 2 years (n=8)	62.5 (5)	62.5 (5)	25 (2)

*Values shown as % (n) unless otherwise specified.

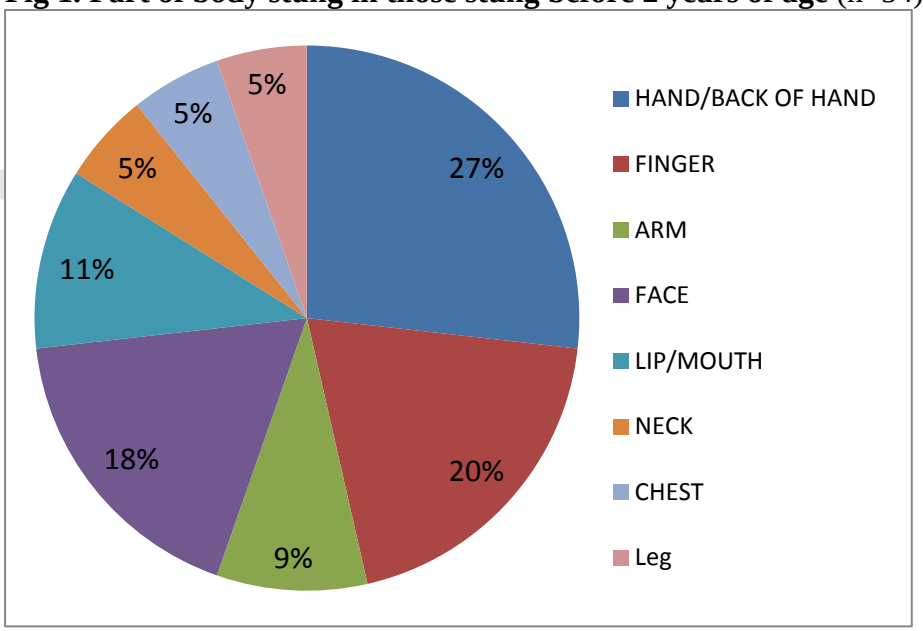
Table 4. Comparison between those who had been stung and those not stung by 5 years

	Previously stung (n=268)	**Not previously stung** (n=958)	**p-value**
Sex			
Girls	115 (42.9)	482 (50.3)	0.024
Boys	153 (57.1)	476 (49.7)	
Activity Level			
Active for more than two hours/day	135 (50.4)	468 (48.9)	0.679
Active for less than two hours/day	133 (49.6)	490 (51.1)	
Home Address			
Urban	31 (54.4)	138 (55.4)	
Rural	26 (45.6)	111 (44.6)	0.884
Skin Prick Tests			
Bee positive at two years	3 (1.4)[1]	5 (0.5)[1]	0.174
Bee positive at five years	0 (0.0)	1 (0.1)	1.000
Wasp positive at two years	1 (0.5)[1]	1 (0.1)[1]	0.215
Wasp positive at five years	0 (0.0)	3 (0.4)	1.000

*Values shown as N (%) unless otherwise specified.

[1]While 9 were positive to bee and 3 were positive to wasp at 2 years, not all had a documented sting history due to loss to follow-up

Fig 1. Part of body stung in those stung before 2 years of age (n=54)



Appendix A

Questionnaire for nested observational study
BASELINE NUMBER:
Date of Birth:
Consent:
1. Has your child, recruited into BASELINE, ever been stung by bee or wasp?
YES NO
If you answered **YES** to question 1, please complete the rest of the questionnaire.

2. How many times has your child been stung by a bee or a wasp? _____

3. Please describe the event: (If more than once, we will complete the questions for each sting in turn)
Age in months when stung _____
Month of year when stung _____
Location (home indoors, home outdoors, away from home indoors, away from home outdoors, other)
_____
What was your child doing at the time of the sting:
_____
Body part stung, (eg finger face, neck, etc): _____

4. Do you think it was a bee or wasp? (Note: Wasps can sting more than once, so it is possible to see more than one puncture mark; Bees die after stinging, often leaving the sting in the site or the insect body can be found nearby)
Bee Wasp Not certain

5. Did your child have swelling next to this sting site that was larger than 5 cm (2 inches)
diameter and lasted for more than 2
days?
YES NO
How big in diameter was the swelling? _____
How long did the swelling last? _____

6. Did your child have any skin reactions such as a rash, hives, or swelling in other body parts
(except for the sting site) within 1 (one) hour following the sting?
YES NO
If **YES**: Describe the reaction: _____
Where was the reaction located on the body? _____
How long did the reaction last? _____

7. Did your child experience any of the following difficulties within 1 (one) hour following this sting: (please circle the relevant symptoms)
Breathing trouble (including wheeze)
Asthma attack
Abdominal pain
Loss of consciousness
NONE of these

8. Did you bring your child to a healthcare professional because of this sting?
Hospital GP Pharmacist
Other (specify) _____
NONE

9. Did your child receive any treatment for the sting? (ice, creams, oral medications etc.)
YES NO
If **Yes**: What treatment was given: _____

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