





Frequent Bee Stings May Promote More Severe Allergic Reactions in Children with Large Local Reactions

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ABSTRACT

Objective: Risk of severe systemic reactions (SR) with subsequent hymenoptera stings for patients who had a large local reaction (LLR) or only cutaneous symptoms is considered to be negligible but recent studies report cases who have experienced more severe reactions. We aimed to evaluate the frequency of reactions that are more severe than previous ones after re-sting for children with hymenoptera venom hypersensitivity reactions.

Materials and Methods: Children who had attended four pediatric allergy clinics for reactions due to hymenoptera sting were questioned for previous and subsequent stings by phone call. Number of stings, characteristics of reactions, type of bee were recorded. Whether they had a reaction more severe than the first reaction with subsequent stings was evaluated.

Results: By phone call, 148 children who had LLR or SR were contacted. Of these 55 had a subsequent sting after LLR or SR and 49 had had reactions more than once. In 29 patients (59.1%), there was a more severe subsequent reaction. Twenty (52.6%) of 38 children with LLR had Grade II-III SR with subsequent stings. Age, gender, type of hymenoptera, living place, presence of concomitant allergic reaction in children and/or parents of patients who had or did not have a more severe reaction with subsequent stings were not different between two groups. Median number of hymenoptera stings and sequence of the subsequent sting causing the most severe reaction were higher among patients who had a more severe reaction ($p < 0.001$, $p < 0.001$ respectively).

Conclusion: Our results show that we may be underestimating the risk of more severe reactions with subsequent stings for children.

Keywords: Large local reaction, hymenoptera venom, hypersensitivity, severe systemic reactions

INTRODUCTION

Hymenoptera venom hypersensitivity (HVH) is one of the leading causes of anaphylaxis and is an important health problem for children. The prevalence of being stung by hymenoptera species is reported as 37.5% in children

up to 14 years of age, and the rate of systemic sting reactions in epidemiological studies in Europe ranges between 0.15% and 3.4% in children (1). In a study conducted in our country, it was found that 1% of the total admissions to a pediatric emergency department in June, July and

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August 2005 were cases of bee stings (2). According to the European network of severe allergic reactions (NORA), 20.2% of all the anaphylaxis cases in children were due to insect venom (3). While it can cause life threatening reactions, it is hard to prevent new stings and therefore new reactions due to HVH. Venom immunotherapy (VIT) is suggested and can be life saving for children who had experienced severe systemic reactions (SR) due to HVH (4). However, it is not well defined how to treat children who had mild SRs and large local reactions (LLR) after hymenoptera stings.

It is generally accepted that patients and especially children will not experience a reaction that is more severe than the previous one with subsequent stings. Based on the assumption of a negligible risk of more severe SRs, the American College of Allergy, Asthma & Immunology (ACAAI) - American Academy of Allergy, Asthma & Immunology (AAAAI) and the European Academy of Allergy and Clinical Immunology (EAACI) guidelines report adrenalin autoinjector (AAI) prescription for children presenting with LLRs as “generally not necessary” and do not suggest VIT for children who had SRs restricted to cutaneous symptoms unless there are special circumstances such as risk of frequent exposure, underlying cardiovascular and respiratory disease, etc. (4,5).

The underlying mechanism of LLR can be IgE, cell-mediated or even toxic. Most patients with LLR may have significant venom sensitivity. Patients with a history of LLRs have an approximately 7% chance of SR to a future sting (range, 4%-15%) in both adults and children (5-7). Although earlier studies reported a negligible risk, more recent studies documented a considerable number of patients who had more severe reactions with subsequent stings (8-11). Recently, the reactions of 225 patients (adult and children) who had LLRs when they experienced hymenoptera sting and were re-stung during the study period were evaluated by Bilò et al. They reported that 24% had SRs after re-sting (12).

In our previous study about the characteristics of children with anaphylaxis, there were 31 children with hymenoptera venom anaphylaxis and twenty of them had had a reaction with a previous sting before they attended our clinic with anaphylaxis. While 9 of the previous reactions before anaphylaxis were also anaphylactic reactions, 3 had LLRs and 3 had angioedema as a previous reaction (13). Thus, we aimed to evaluate the frequency of reactions that

are more severe than previous ones after re-sting for children with HVH reactions. Gathering detailed information about the subject will help us to define children who are in need of an AAI prescription and VIT .

MATERIAL and METHODS

The study was conducted in 4 pediatric allergy clinics (Ankara, Malatya, İzmir, Tokat) between January 2018 and December 2018. Children who had attended the clinics for reactions due to hymenoptera sting during January 2010-December 2018 period were included in the study. Age at reaction, gender, type of the hymenoptera, characteristics of reaction, laboratory tests at the time of reaction, and concomitant allergic diseases of the children and parents were recorded from the patient files.

Patients included in the study were questioned for previous and subsequent stings by phone call. For patients who were receiving VIT, only reactions before treatment were questioned. If present, the number of hymenoptera stings, characteristics of reactions, and type of the hymenoptera were recorded. The living place of the patient was noted as “in city” or “other-village, district. For patients who were stung for 4 times or less, every reaction for every sting was given in detail. For patients who were stung more than 4 times, characteristics of the most SR with re-sting was recorded.

For patients who had reported more than one reaction, whether they had a reaction more severe than the first reaction with subsequent stings was evaluated. Characteristics of the patients who had or did not have a more severe reaction were compared. The very first reaction the patient had with a hymenoptera sting was recorded as the “first reaction”.

The study was approved by the ethical review committee of the University of Health Sciences, Ankara Child Health and Diseases, Hematology, Oncology Training Research Hospital (EC number: 2018-153). Oral consent was obtained from caregivers of patients before enrollment in the study.

Type of the reaction

Induration and hyperemia at the site of the sting that was smaller than 10 cm and lasting for less than 24 hours was not recorded as a reaction. Reactions larger than 10 cm diameter and lasting for 24 hours or longer were recorded as LLR (4,7).

Any reaction appearing far from the sting site was recorded as SR. Systemic reactions are classified according to the Muller classification that was modified by Ring and Messmer (14).

Grade I: generalized skin symptoms (urticaria, angioedema)

Grade II: mild to moderate respiratory, cardiovascular and gastrointestinal symptoms

Grade III: anaphylactic shock, loss of consciousness

Grade IV: cardiac arrest, apnea

SPT and Venom Specific IgE Analysis

For patients who had systemic reactions, Epidermal SPTs were performed when available. Testing was performed using allergen extracts (ALK-Abello, Madrid, Spain) in 0.001, 0.1 and 1 mcg/ml concentrations along with a positive control (10 mg/dl of histamine phosphate) and a negative control (0.9% sterile saline). Diameters of the indurations were measured horizontally and vertically. Indurations with an average diameter of at least 3 mm greater than the negative control were considered positive. Intradermal tests could not be performed because of unavailability.

For patients who had systemic reactions, *Vespula* and *Apis* allergen-specific IgE antibody measurements were performed when available. The ImmunoCAP (Thermo Fisher Scientific, Uppsala, Sweden) and Immulite 2000 assay system (Siemens Healthcare Diagnostics, NY) were used and results were considered positive when levels were equal to or greater than 0.35 kU/L.

Statistical Methods

Statistical analyses were performed using SPSS 22 (IBM Corporation, Armonk, NY). Numbers and percentages are reported for discrete variables and means and standard deviations for continuous variables. Values are presented as means and standard deviations for data demonstrating a normal distribution and as medians and interquartile ranges (IQR) for data not demonstrating a normal distribution. The χ^2 test was performed to compare nonparametric data, the Mann-Whitney test data without a normal distribution, and the independent t test for continuous data with a normal distribution. A value of $p < 0.05$ was considered statistically significant.

RESULTS

During the study period, 283 patients who were seen for hymenoptera stings were found from hospital records and 228 of them could be contacted by phone. According to parent reports, 80 children had only a local reaction smaller than 10 cm. Of the remaining 148 patients who had at least one reaction (LLR or SR), 93 had a reaction (LLR or SR) only once and were not stung after that reaction (Figure 1). The families of 14 (6.1%) of the patients were beekeepers.

Fifty-five patients had at least one subsequent hymenoptera sting after their first reaction. The mean age of these patients was 15.34 ± 3.28 years (41 males) and median sting number was 3 (IQR:2-5). Hymenoptera type was reported as *Vespula* in 28 (51%) and *Apis* in 23 (41.8%), 4 patients could not define the hymenoptera type.

When laboratory results were evaluated, it was seen that 9 patients defined the hymenoptera type incorrectly. Median *Vespula* specific IgE value was 4.61 kU/L (IQR:1.71-12), median *Vespula* skin prick test diameter was 4.3 (IQR:1.5-12) mm and median *apis* specific IgE was 14 (IQR:3 -36) kU/L.

In 29 (52.7%) of these 55 patients who had a sting after an LLR or SR, there was a subsequent reaction that was more severe than the first one. Of the patients who had LLR as initial reaction, 6 patients (15.8%) had grade I SR, 2 (5.2%) had grade II SR and 18 (47.3%) had grade III SR with subsequent stings; thus 68.4% of these children had a more severe reaction and 52.5% of them had a grade II-III SR with subsequent stings after LLR. Of the patients who had grade I SR as an initial reaction, two patients (50%) had grade II SR. One patient had grade III SR with subsequent sting after grade II SR as initial reaction (Figure 2).

When patients who had or did not have a more severe reaction with subsequent stings were compared, the age, gender, type of hymenoptera, living place, presence of concomitant allergic reaction in children and/or parents were not different between the two groups. Median number of hymenoptera stings was higher among patients who had a more severe reaction with subsequent stings ($p < 0.001$). Sequence of the subsequent sting that had caused the most severe reaction was higher in the group that had a more severe reaction with re-sting ($p < 0.001$) (Table I).

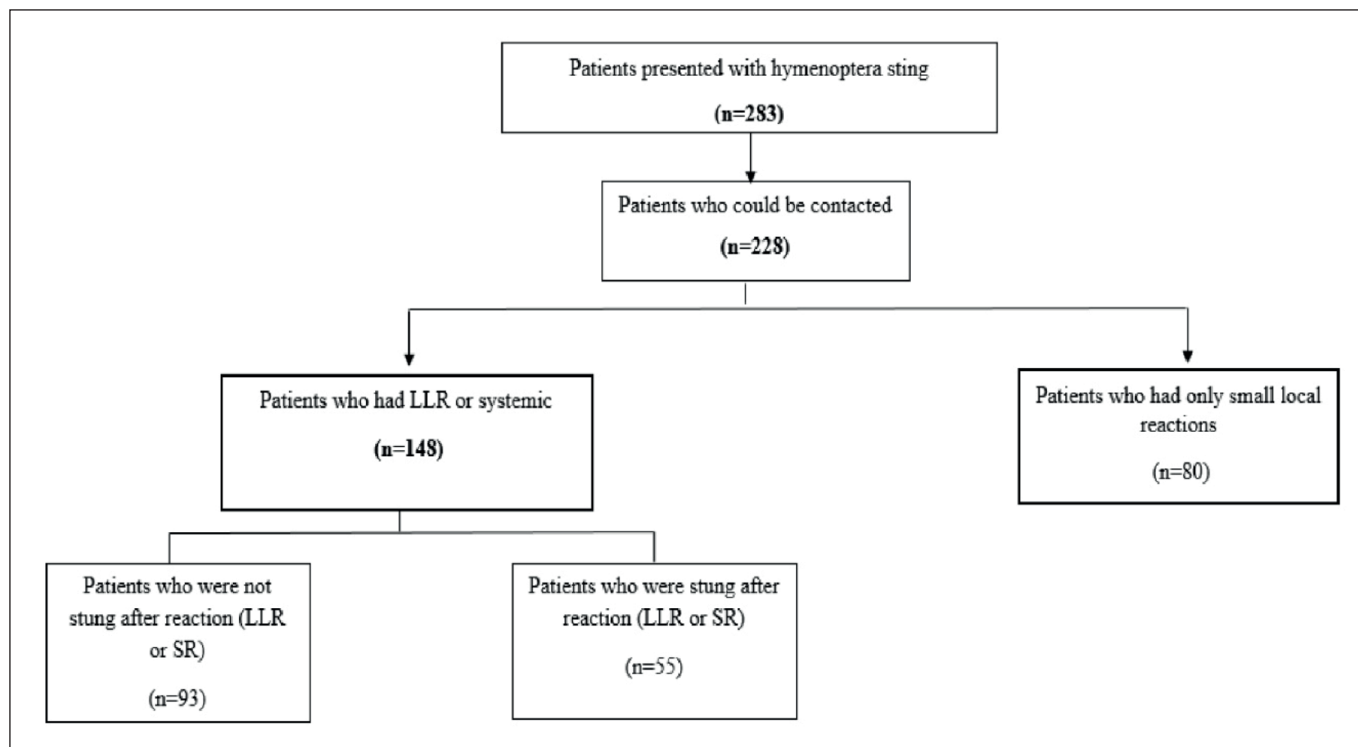


Figure 1. Algorithm of the study patients.

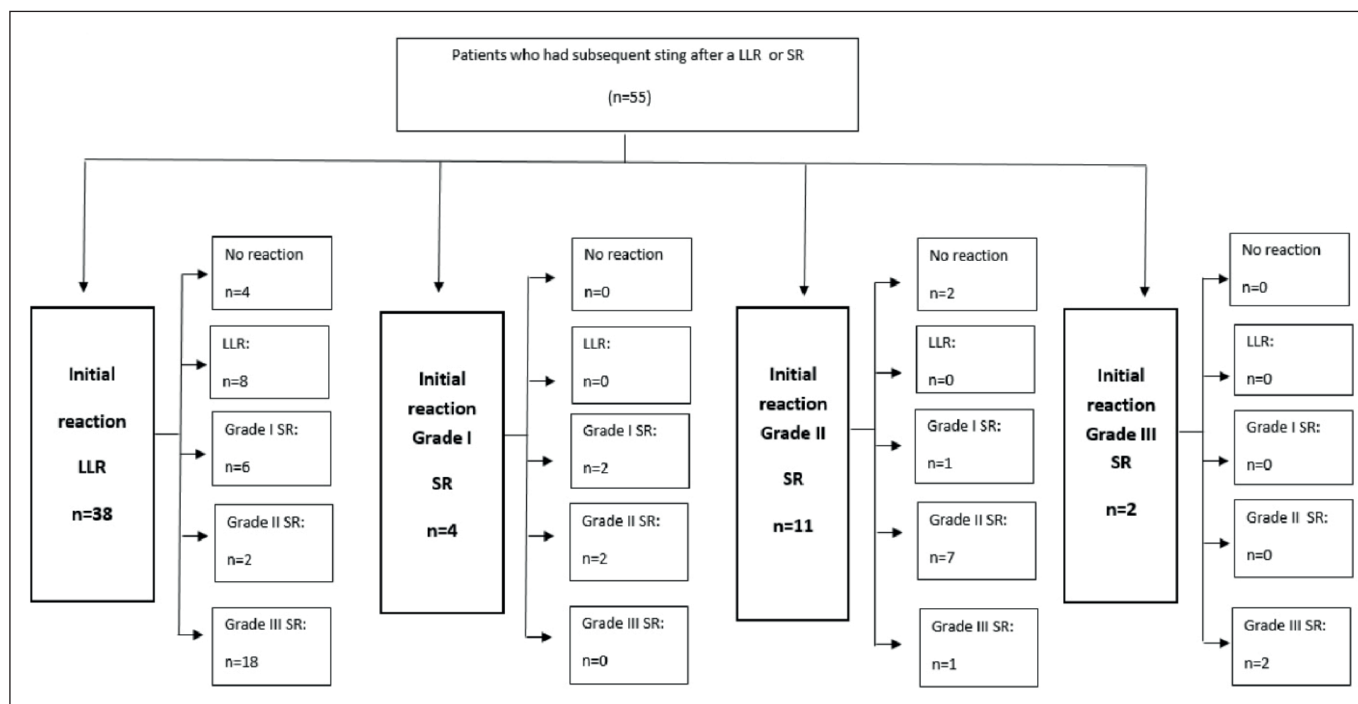


Figure 2. Most severe subsequent reactions of patients who had at least one subsequent reaction after an LLR or SR.

Table I: Comparison of patients who had and did not have a more severe reaction with subsequent stings.

	Patients who had a more severe reaction n=29	Patients who did not have a more severe reaction n=26	p
Gender n, %			
Male	23 (80)	18 (69)	0.51
Age (years), Mean±SD (min-max)	15.59±3.36	14.9±3.7	0.28
Type of hymenoptera, n (%)			
Apis	11 (37.9)	7 (27)	0.12
Vespula	18 (62.1)	19 (73)	
Number of stings, Median (IQR)	4 (3-6)	2 (2-3)	<0.001
Rank of subsequent sting that had caused the most severe reaction	4 (2.5-6)	1 (1-3)	<0.001
Allergic disease in family, n (%)	2 (6.9)	3 (11.5)	0.36
HVA in family, n (%)	2 (6.9)	3 (11.5)	0.65
Presence of allergic disease, n (%)	6 (20)	9 (34.6)	0.36
Living place, n (%)			
City	13 (44.8)	15 (57.7)	0.56
Village and district	16 (55.2)	11 (42.3)	
Vespula Specific IgE, Median (IQR)	4.36 (1.20-17.6)	1.81(1.37-8.57)	0.23
Apis Specific IgE, Median (IQR)	20.3 (6.6-36)	2.18 (0.69-75.59)	0.09

We have also evaluated the time period between the first reaction and the most severe subsequent reaction. Parents of children who had more than 4 stings could not recall the time period so we have taken this parameter only for children who had 4 or less stings. Of the 55 patients that were stung after a reaction (LLR or SR), 40 had 4 or less reactions. Within these 40 patients, for children who had a more severe reaction, the median time period was 2 (1.5-3) years, for patients who did not have more severe reaction with a subsequent sting, the median time period was 2 (1-2) years ($p=0.46$).

DISCUSSION

In this study, we have evaluated 148 children who were seen in the hospital for an LLR or SR with hymenoptera stings: 93 of them were not stung after the reaction and 55 had at least one subsequent reaction after a reaction (LLR or SR). We have documented that with subsequent stings, 29 (52.7%) of these 55 children had a reaction that was more severe than a previous one.

Based on the assumption of a negligible risk of more severe SRs, ACAAI-AAAAI and EAACI guidelines report adrenalin autoinjector (AAI) prescription for children presenting with LLRs as “generally not necessary” and

do not suggest VIT for children who had SRs restricted to cutaneous symptoms unless there are special circumstances such as risk of frequent exposure, underlying cardiovascular and respiratory disease, etc. (4,5).

Although earlier studies conducted in small groups have reported a negligible risk for more severe reactions with later hymenoptera sting, more recent studies presented cases who had more severe reactions with subsequent stings. In 1987, Savliwala and Reisman reported that 29 patients (adult and children) did not have any reaction with repeat stings within 5 years after a systemic reaction (8). Valentine et al. followed their patients (all children) who had cutaneous reactions with hymenoptera sting and did not report any reactions with re-sting that is more severe than the first reaction (9). However, in the following years, Golden et al. presented 6 children who had mild SR with their first sting but had a moderate SR when they were re-stung (10). In 2015, Lange et al. reported that 15% of children who had grade I reaction and 25% of children who had grade II SR during their first sting experienced grade III SRs when they were re-stung (11). Recently, a report of 225 patients (adult and children) who had large local reactions when they experienced hymenoptera sting and were re-stung during the study period was evaluated

by Bilò et al. They reported that 24% had SRs after re-sting but did not give special consideration about children (12). In our previous report discussing the characteristics of children with anaphylaxis, we have reported that 20 of 31 subjects with hymenoptera venom anaphylaxis had experienced a reaction with a previous sting and while 9 of the previous reactions were anaphylaxis, 3 had LLRs and 3 had angioedema before they had experienced anaphylaxis (13). Our present study, revealed that 52.7% of children had a more severe reaction with re-sting; 52.6% of children presenting with LLR had a grade II- III SR and 2 of 4 children who presented with a SR that did not exceed cutaneous symptoms had experienced a more severe SR with re-sting. Our data supports the idea that the risk of a more severe reaction with subsequent hymenoptera stings after LLRs and SRs restricted to cutaneous symptoms is not negligible.

In the study by Bilò et al, a mild/moderate SR (grade I or II) occurred in 29 (13%) and severe SR (grade III or IV) in 25 (11%) of patients with a previous sting (12). Of the 38 children who had LLRs as a first reaction in our study, 6 (15.7%) had experienced grade I SR, 2 (5.2%) had grade II SR and 18 (47.3%) had grade III SRs with re-sting. In total, 68.4% of all children who had LLR as initial reaction experienced a systemic reaction with re-sting and 52.6% had severe SR in our study.

We have evaluated factors predicting children that are at risk of more severe subsequent reactions with re-sting. Characteristics of the patients such as age, gender, presence of concomitant allergic disease, and presence of allergic disease and/or HVH in the family were not different between groups. Although more severe reactions with re-sting were more common in the group stung by Apis (37.9% vs, 27%), the difference did not reach statistical significance. Bilò et al. also did not define these parameters as risk factors (12). The number of stings and the sequence of the sting causing the most severe reaction was higher in the group with more severe subsequent reactions ($p < 0.001$ and $p < 0.001$ respectively). Children that are prone to more frequent stings may be at higher risk of more severe reactions with re-sting.

When laboratory tests were compared, specific and total IgE levels were also not reported to be related to the risk of subsequent SRs in our study and the study by Bilò et al. (12). However, they have reported that skin test reactivity during ID tests, especially at $0.001 \mu\text{g/mL}$ concen-

tration, had predictive value for defining patients who are going to have systemic reactions. Intradermal tests could not be performed for our patients so we could not define the predictive value of this test for our study group in the mentioned study.

The main limitation of our study is the retrospective nature of the study as this may have caused recall and reporting bias. However, we think that parents could recall and discriminate between systemic reactions (especially severe ones) from LLRs. Laboratory tests such as sIgE levels had not been measured and skin tests had not been performed at presentation for patients who had presented with LLRs as there was no indication. Further prospective studies measuring sIgE and basal tryptase levels and performing prick and intradermal tests to all children at presentation and observing all subsequent reactions with re-sting might predict the risks of more severe reactions better. This study reveals that 58.2% of children with allergic reactions to stings who are subsequently stung again may experience a more severe reaction after LLRs or SRs limited to mild skin symptoms as initial reaction. As a matter of fact, 52.6% of patients with LLRs had a grade II-III SR with subsequent stings. Our results show that we may be underestimating the risk of more severe reactions with subsequent stings for children. Management strategies of mild reactions with hymenoptera stings should be re-evaluated in the light of more detailed studies on the subject.

Authorship Contributions

Concept: **Muge Toyran, Sehra Birgul Batmaz, Selin Tasar, Emine Dibek Misirlioglu**, Design: **Muge Toyran, Ilknur Kulhas Celik, Hakan Guvenir, Can Naci Kocabas**, Data collection or processing: **Muge Toyran, Ilknur Kulhas Celik, Selime Ozen, Sehra Birgul Batmaz**, Analysis or Interpretation: **Ilknur Kulhas Celik, Selin Tasar, Demet Can, Ersoy Civelek**, Literature search: **Muge Toyran, Ilknur Kulhas Celik, Hakan Guvenir, Selime Ozen**, Writing: **Muge Toyran, Ersoy Civelek, Can Naci Kocabas, Emine Dibek Misirlioglu**, Approval: **Muge Toyran, Ilknur Kulhas Celik, Hakan Guvenir, Selime Ozen, Sehra Birgul Batmaz, Selin Tasar, Demet Can, Ersoy Civelek, Emine Dibek Misirlioglu, Can Naci Kocabas**.

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