

Long-term follow-up of re-sting reactions in children with moderate to severe venom hypersensitivity

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Abstract Few data exists about re-sting reactions and their prognosis in children with moderate to severe venom hypersensitivity. The reasons behind not consenting to or prematurely ending venom immunotherapy (VIT) and the preparedness of children who refused or quit VIT for future moderate–severe systemic reaction (SR) to re-stings have not been studied. Data on children with moderate to severe SR after Hymenoptera stings was collected for a 17-year period using our database. A standardized questionnaire was administered to patients who accepted to be interviewed at the clinic. These patients were evaluated in terms of their preparedness for future moderate–severe SR to re-stings. A total of 55 children, 75 % of whom commenced on VIT, were included in the analysis. Different reasons exist for not consenting to VIT; the most common of which is living at a distance from the allergy center. There were no differences in terms of the number of re-stung patients (27.7 and 27.2 %, respectively) and moderate–severe SR (60 and 16.6 %, respectively) between children

who prematurely ended or who did not consent to VIT and children who completed VIT. Sixty-four percent of the children who refused or discontinued VIT were not prepared for future moderate–severe SR to re-stings.

Conclusion: Long-term prognosis for re-sting reactions is good in children with moderate to severe SR to venoms. Some of the reasons behind refusing or discontinuing VIT may be related to quality of life issues. Preparedness of children who refused or discontinue VIT in emergencies is very low.

Keywords Auto-injector · Children · Re-sting · Quality of life · Venom hypersensitivity

Abbreviations

BSACI	British Society for Allergy and Clinical Immunology
LLR	Large local reaction
SIgE	Specific IgE
SRs	Systemic reactions
QoL	Quality of life
VIT	Venom immunotherapy

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Introduction

Hymenoptera stings may cause a wide range of reactions from local to life-threatening systemic reactions. Systemic reactions (SRs) due to Hymenoptera stings are usually mild and confined to the skin in children [6]. The prognosis for isolated cutaneous SR is good and current guidelines do not recommend venom immunotherapy (VIT) for this group [4, 6]. Venom immunotherapy is the single specific treatment for patients with a history of moderate to severe SR to a

Hymenoptera sting [4]. There is few data about the long-term follow-up of moderate to severe SR in children in terms of re-sting reactions [3, 5, 8]. The reasons for not consenting to or prematurely ending VIT have not been described in previous reports on children. Also, to our knowledge, no study has specifically evaluated the preparedness of children who refused or quit VIT for future moderate to severe SR to re-stings. Therefore, this study aimed to evaluate re-sting reactions and their prognosis in children with moderate to severe SR. As secondary aims, the authors wanted to determine the reasons behind not consenting or prematurely ending VIT and the preparedness of children for re-sting reactions.

Methods

Patients

We made a retrospective chart review for a 17-year period between September 1996 and September 2012 of patients referred to our clinic for assessment of anaphylaxis with a history of Hymenoptera sting. Children who had moderate to severe SR after Hymenoptera stings according to the British Society for Allergy and Clinical Immunology (BSACI) guideline for diagnosis and management of hymenoptera venom allergy were enrolled [6]. We collected demographic data, data on the patients' medical history, and the results of any Hymenoptera-specific diagnostic tests from the medical records. All patients and/or their parents were called via the last known telephone number, and if we could not reach the patients in this way, we searched the telephone number database. The patients and their parents who could be contacted were invited for an interview in the clinic on August 2013. A questionnaire about re-sting and reaction history (time, type of Hymenoptera, severity and treatment of re-sting reactions) was filled out. At this follow-up visit, interviewed patients were checked by a trainer for their ability to use an adrenaline auto-injector. The Gazi University Hospital Ethics Committee approved the study, and a written informed consent was obtained from all patients.

Diagnosis of IgE-mediated venom hypersensitivity

The diagnosis of anaphylaxis was based on clinical history, positive prick and/or intradermal skin tests, and/or detection of specific IgE (sIgE) to the type of venom involved.

Skin tests

Skin tests were performed with *Apis* and *Vespula* (*Apis mellifera*, Guepes *Vespula*, Stallergenes, France) at least 4–6 weeks after the sting reaction at the time of diagnosis. Skin prick tests (SPT) were performed with concentrations

ranging from 1.0 to 100 µg/ml; if negative, intradermal injections of 0.02 ml venom were performed with 10-fold dilutions ranging from 0.001 to 1 µg/ml and 0.02 ml on the volar surface of the forearm along with positive and negative controls (histamine and saline solution).

In vitro tests

Serum sIgE levels to *Apis* and *Vespula* venom were measured with the Immuno CAP system (Phadia AB, Uppsala, Sweden) in accordance with the manufacturer's instructions. Specific IgE levels to *Apis* and/or *Vespula* >0.35 kU/l were considered positive. The measurement of serum sIgE was performed at least 4 weeks after the sting reaction.

Severity of reactions

Allergic reactions were graded according to the severity. An area of indurations with a diameter of 10 cm that peaks between 24 and 48 h and then subsides is referred to as a large local reaction (LLR). The severity of initial and re-sting SRs was graded according to the BSACI guideline (Table 1).

Education about prevention and adrenalin auto-injector use

An adrenaline auto-injector was prescribed to all children with moderate to severe SR, and all patients were trained for appropriate use at the time of diagnosis. Both verbal and written instructions of auto-injector use and education to avoid stinging insects were given to all patients and to their parents.

Immunotherapy

Venom immunotherapy was recommended to all patients in whom moderate–severe SR to Hymenoptera sting was confirmed. All patients were treated with the same immunotherapy products (*A. mellifera*, Guepes *Vespula*, Stallergenes, France). An experienced nurse observed by allergists and using the conventional protocol performed the immunotherapy at our

Table 1 Classification of systemic allergic reactions to Hymenoptera stings [6]

Severity	Features
Mild	Pruritus, urticaria, erythema, mild angio-edema, rhinitis, conjunctivitis
Moderate	Mild asthma, moderate angio-edema, abdominal pain, vomiting, diarrhea, minor, and transient hypotensive symptoms (light-headedness, dizziness)
Severe	Respiratory difficulty (asthma/laryngeal edema), hypotension, collapse, or loss of consciousness; rare: double incontinence, seizures, loss of color vision

Table 3 Characteristics of patients

	<i>Apis</i>	<i>Vespula</i>	Total
Number of patients, <i>n</i> (%)	11 (20)	44 (80)	55 (100)
Male gender, <i>n</i> (%)	9 (81.8)	30 (68.1)	39 (70.9)
Mean age at diagnosis, years ($\pm$ SD)	8.8 $\pm$ 3.8	10.3 $\pm$ 3.8	10 $\pm$ 3.9
Type of reactions prior to the index SRs, <i>n</i> (%)			
No recall of a bee sting	1 (9.1)	13 (29.5)	14 (25.4)
Local reactions	5 (45.5)	20 (45.5)	25 (45.4)
Large local reactions	—	1 (2.3)	1 (1.8)
Systemic reactions	5 (45.4)	10 (22.7)	15 (27.2)
Median observation period, years (range)	4 (1.5–17.1)	7.8 (1–16.9)	5.6 (1–17.1)
No. of patients who commenced VIT, <i>n</i> (%)	6 (54.5)	35 (79.5)	41 (74.5)
No. of patients who completed VIT, <i>n</i> (%)	2 (33.3)	20 (57.1)	22 (53.6)
No. of patients who are still under VIT, <i>n</i> (%)	3 (50)	12 (34.2)	15 (36.5)
No. of patients who prematurely ended VIT, <i>n</i> (%)	1 (16.6)	3 (8.5)	4 (9.7)
No. of patients re-stung during follow-up, <i>n</i> (%)	2 (18.1)	16 (36.3)	18 (32.7)
SR systemic reaction, VIT venom immunotherapy	No. of re-stings during follow-up, <i>n</i>	3	32
		32	35

clinic. Subcutaneous injections were given weekly for 16 weeks until the maintenance dose of 100 μ g/ml was reached. Then, the maintenance dose was continued for 5 years at 4–6-week intervals. After each injection, patients were kept under medical observation for at least 30 min in the clinic, where full emergency resuscitation equipment was available. All patients were re-evaluated regularly at 3-month intervals until stopping VIT after a duration of 5 years. If the patient quit VIT before 5 years, it was defined as prematurely ended VIT. Venom immunotherapy was ceased in patients who continued VIT for 5 years and who did not have any SR to a sting or venom injection during the VIT.

Statistical analysis

The Statistical Package for Social Sciences (SPSS) 15.0 software (SPSS, Inc. Chicago, IL) was used to perform the statistical analysis. A descriptive analysis was used to determine the characterization of patients. Descriptive statistics were expressed as frequency and percentage for categorical variables, where as quantitative data were expressed as mean standard deviation for normally distributed variables and as medians (min–max) for non-normally distributed data. Group comparisons were established using the Mann–Whitney *U*-tests for medians, and the Student's *t* test for means (and standard deviations). The Pearson chi-square test and/or Fisher's exact test were used to compare categorical variables between the groups. A two-sided value of $p < 0.05$ was considered statistically significant.

Results

Demographics

A total of 60 medical records with moderate–severe SR to hymenoptera sting were found during the 17-year period. Contact could not be made with five of these patients; therefore, only the 55 children who could be contacted were included in the study. All patients contacted either by telephone and/or at their regular visits were interviewed face-to-face in August 2013 at our clinic. The characteristics of the patients, their VIT, and re-sting status are shown in Table 3. Fourteen patients (25.4 %) did not consent to VIT, and four patients prematurely ended VIT for specific reasons (Table 2).

Table 2 Reasons for not consenting to or prematurely ending VIT ($n=18$)

Reasons for not consenting	
Living at a distance from allergy center	5
Does not think it is necessary	3
Injection phobia	2
To think it would be safe to carry an auto-injector	1
Parents think that the child is too young to get injections regularly	1
Has to abstain from school for VIT	1
Thinks that removing a bee nest is enough	1
Reasons for prematurely ending	
Living at a distance from allergy center	2
Nothing happened after a re-sting during the first year of VIT	2

Follow-up

of VIT (13/41, 31.7 %). There were no LLR or SRs in any of the re-stings.

Re-sting reactions

All reactions to re-stings during the follow-up period are shown in detail in Fig. 1.

During VIT (n=41)

There were no re-stings in the induction phase. Thirteen patients (under VIT with *Vespula* 12, *Apis* 1) were re-stung 18 times with the same species during the maintenance phase

After completion of VIT (n=22)

Median follow-up time after VIT in children who completed a treatment of 5 years was 8.4 years (4 months–11 years). Six patients who completed VIT with *Vespula* were re-stung with the same species 10 times over a period of 1–10 years after completion of VIT (27.2 %). Systemic reaction occurred in only one (16.6 %). This patient did not react to two re-stings that occurred 1 and

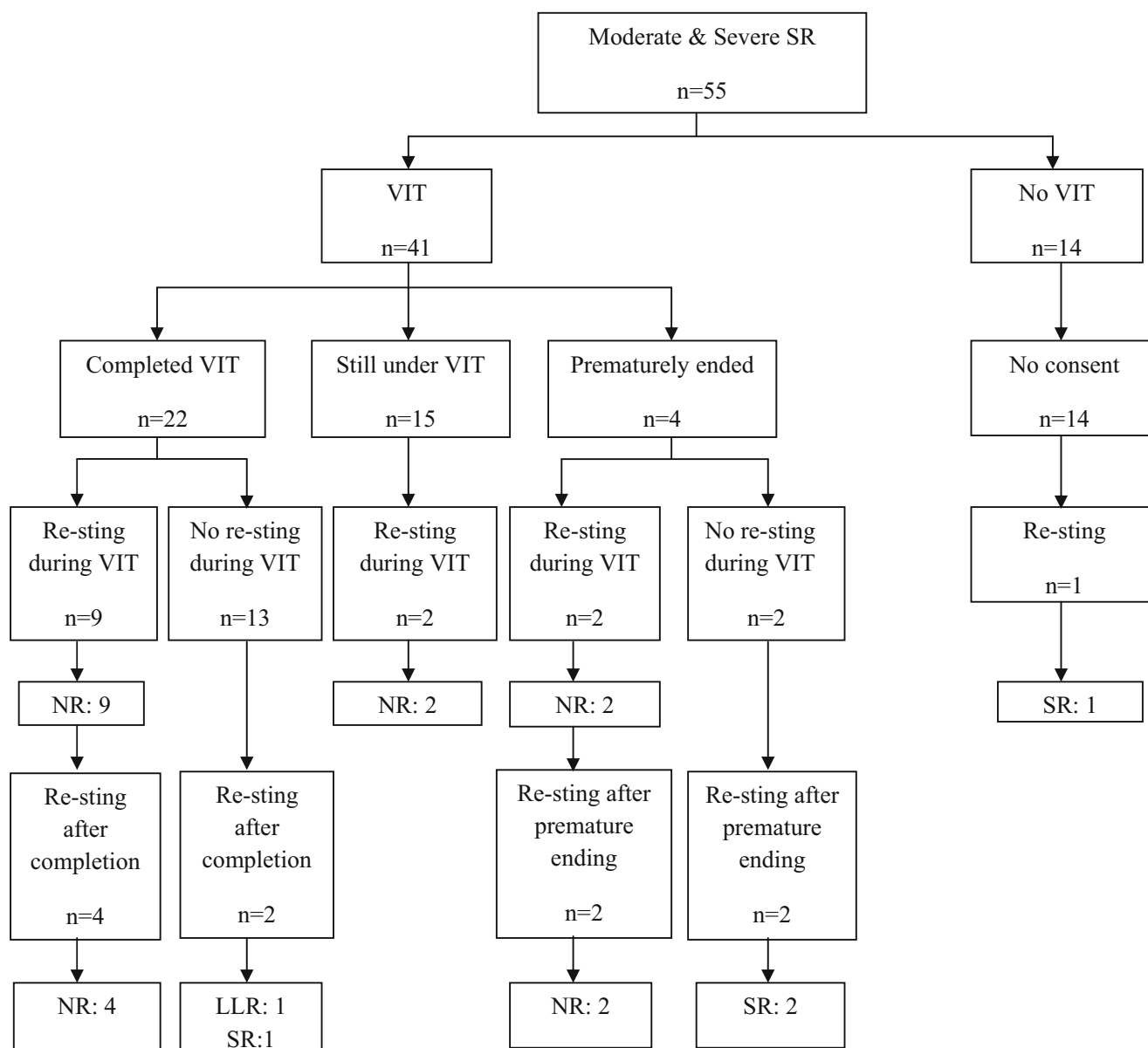


Fig. 1 Re-sting reactions in children with moderate to severe venom hypersensitivity during follow-up. VIT venom immunotherapy, NR no reaction, SR systemic reaction, LLR large local reaction

4 years later but presented with moderate to severe SR to a third re-sting in the ninth year.

Patients who did not consent or prematurely ended VIT (n=18)

Among patients who did not consent to VIT (*Vespula* nine and *Apis* five children), there was only one patient who was sensitized to both *Apis* and *Vespula* but described and diagnosed as severe SR only with *Vespula* at the time of application to our clinic. This patient was re-stung by *Vespula* twice and once with *Apis* 3 years after the diagnosis. This patient experienced severe SR in all three re-sting events.

Four patients prematurely ended VIT after 18, 26, 30, and 46 months (Table 3). These patients were re-stung six times over 1 to 12 years after they quit VIT. Among them, one patient who quit in 18 months and another who quit in 46 months experienced SR at the same severity with an index reaction to re-stings 10 and 11 years after the premature end of VIT.

We took children who prematurely ended VIT with children who did not consent VIT into a single group ($n=18$) and compared them with children who completed VIT ($n=22$) to determine the number of patients who were re-stung and who experienced SR after the VIT period. There was no difference in terms of the number of re-stung patients (27.7 and 27.2 %, respectively) and SR (60 and 16.6 %, respectively) between the two groups ($p>0.05$ for both).

Management of SR with re-stings

During the follow-up, four patients were re-stung and six moderate–severe SR were experienced. Only one of these patients was carrying an adrenaline auto-injector; however, this patient was afraid to use it in three episodes and did not consent to VIT. Although systemic antihistamines and corticosteroids were used in all six episodes, only two of them were treated with intramuscular adrenaline in the hospital.

Adrenaline auto-injector competency

All 15 patients who were still under VIT were carrying auto-injectors, and all were competent with its use. Only five of the 18 patients who did not consent to and who prematurely ended VIT were coming to follow-up visits regularly once a year at our clinic, carrying an adrenaline auto-injector, and were competent in its use (27.7 %). The rest of the patients in this group did not come to follow-ups regularly and did not carry an adrenaline auto-injector. All of these patients had an adrenaline auto-injector in the first few years of diagnosis, but thereafter, they did not renew the device and were not competent in its use. Six of the 22 patients who completed VIT

were carrying and competent in using the adrenaline auto-injector.

Discussion

This is a retrospective cohort study that evaluated re-sting reactions in children who experienced moderate to severe SR with venom stings in the long-term follow-up. We included all patients with moderate to severe SR who completed or were still under VIT as well as those who did not consent to or prematurely ended VIT. There was no difference with respect to future moderate–severe SR to re-stings between children who completed VIT and children who discontinued or refused VIT. One quarter of the patients did not consent to VIT for different reasons. This study for the first time displayed the reasons behind the refusal or discontinuing of VIT among children and adolescents with moderate to severe SR to venoms as well as the current status of patients about awareness and competency using the adrenaline auto-injector. Also, the study provided additional data that may point to quality of life (QoL) aspects of insect sting allergy, which are both important to patients and are key drivers in relation to the health economics of the treatment.

There have been few reports of moderate to severe SR in children in a follow-up of patients more than 5 years after stopping VIT [3, 8]. In this study, all patients who completed a 5-year conventional VIT were followed up at a median of 8.4 years after VIT. Golden et al. reported the largest case series and the longest follow-up period after VIT in children with moderate to severe venom hypersensitivity [3]. In their study, 43 % of the children who received VIT at an average of 3.5 years and followed up for at least 10 years were re-stung and only two experienced SR (5 %). In our study, 27.2 % of the children who completed VIT were re-stung and only one experienced SR (16.6 %). This difference in the SR rate might be explained by the smaller sample size in our group compared to Golden's. On the other hand, we also found that future moderate–severe SR rates in the rest of our study group were not different than those of the children who completed VIT, similar to the study of Golden et al. [3]. We think that the natural history of re-sting reactions in children in the long term is currently unpredictable regardless of VIT status. Many factors may contribute to this issue, such as the interval that elapsed from the last sting, the patient's immune response at the time of the sting, the dose of venom injected, frequent exposure, the site of the sting, and the elevation of baseline serum tryptase as reported [4, 6, 9].

There are differences in initiating VIT in the current guidelines; VIT is recommended for all adult patients and children ≤ 16 years with moderate–severe SR in the USA, but in Europe, it is recommended only for patients with severe life-

threatening SR [4, 6]. Previous discussions focused on the effectiveness of VIT with respect to preventing future SRs and fatal anaphylaxis from re-stings [2]. However, current discussions have now shifted toward the cost-effectiveness of VIT, particularly in terms of its QoL aspects, since reports have documented that VIT is not seen to be cost-effective when only the direct costs of fatal and non-fatal anaphylaxis outcomes are considered [1, 7]. On the other hand, we think that refusing or discontinuing VIT prematurely may also have effects on the QoL aspects of patients/families. For example, one quarter of patients with moderate to severe SR did not consent to VIT both in our study and in Golden's study [3]. The most frequent reason for refusing consent in our study was living at a distance from an allergy center. Also, half of the patients who discontinued VIT used the same excuse. There are other reasons as well for refusing or discontinuing VIT such as injection phobia, being absent from school or work, difficulty attending appointments, all of which may reflect its relevance to the QoL of patients. Although we could not assess the child or family's QoL or anxiety in relation to insect stings at the beginning and during follow-up due to the retrospective nature of our study, we think that our study provides some insights into this issue. Another important point regarding patients with moderate to severe SR to stings is the acute management of re-stings that cause SR, which is as important as preventive measures, especially in children who refuse or discontinue VIT. Although this is not a new issue in the management of moderate–severe SR with hymenoptera stings, it seems to become one of the most important items on the agenda when there are ongoing discussions about when to offer or initiate VIT. In our series, 64 % (9/14) of children who did not consent to VIT and all of the children who discontinued VIT prematurely were not carrying an adrenaline auto-injector although they had been taught and given education on its use. In these patients, regular visits to allergy clinics may provide better management regarding patient education. There are also gaps in the management of moderate–severe SR by physicians as documented in our study, which may improve by continued medical education. On the other hand, 27 % of children who completed the 5-year VIT, with no known high risk for future reactions, were also carrying the adrenaline auto-injector. These patients explained that they carry the auto-injector just in case, which may reflect ongoing anxiety for future severe SR with re-stings.

Our findings will be of interest to those practicing in this field. There is a relatively small body of literature in this area with respect to children. This is a retrospective cohort study, and it is not possible to control each study parameter, a common limitation of all retrospective studies. Additionally,

the lack of assessment of QoL with objective measures, the small size of the study population, and the recall bias because of the long observation period are the other limitations of this study.

In conclusion, our study provides additional data for the long-term prognosis of re-sting reactions in children with moderate to severe SR to venoms with respect to VIT status. There are different reasons behind refusing or discontinuing VIT among children and adolescents; some of which may be related to QoL issues. Preparedness and competency with an adrenaline auto-injector in emergencies in children who refused or discontinue VIT is very low, which is an issue that certainly needs a multidisciplinary approach.

Conflict of interest The authors declare no conflict of interest.

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