

Hymenoptera venom allergy in a single-center Israeli cohort: Clinical and laboratory characteristics



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Clinical Implications

- Previous reports from Europe showed an increased rate of primary mast cell (MC) disorders as a risk factor for Hymenoptera venom allergy. Our Israeli cohort displayed a low rate of abnormal MC markers, suggesting that this risk factor is not universally present.

TO THE EDITOR:

Hymenoptera venom allergy (HVA) is a typical IgE-mediated systemic reaction. Patients are advised to carry injectable epinephrine and are offered venom immunotherapy (VIT). Previous studies have shown a high prevalence of systemic mastocytosis (SM) among patients with HVA.^{1,2} Consequently, elevated baseline tryptase concentrations (BTC) have been linked to severe sting reactions³ and were shown to be inversely correlated with the safety and success of venom immunotherapy, specifically in patients treated for vespid, rather than bee, venom allergy.

Most of the data on HVA and on risk factors for VIT adverse effects are derived from European studies. We hypothesize that this fact may lead to conclusions that are not applicable to other populations. Therefore, in this study, we aimed to evaluate Israeli subjects who are exposed to the local Hymenoptera species profile in a country with a relatively high density of industrial beehives.

This prospective study included all subjects with HVA under current or planned immunotherapy in a tertiary referral center (Meir Medical Center, Kfar Saba, Israel). Allergic sensitization was confirmed by skin test or radioallergosorbent test in all subjects. After informed consent, BTC was evaluated by the ImmunoCAP method (Phadia 100 system; Phadia-Thermo Scientific, Waltham, Mass) and the peripheral-blood c-Kit D816V mutation was detected by PCR.

Differences between 2 groups were analyzed using the χ^2 test. Metric variables were analyzed using the *t*-test or the Mann-Whitney nonparametric test according to the normality of distribution (Shapiro-Wilk test). $P < .05$ was considered as statistically significant. Analyses were performed using SPSS version 25 (IBM Corporation, Armonk, NY). The study was approved by the local Institutional Ethics Committee

(application number MMC-0100-15) and was registered at the National Institutes of Health site ([ClinicalTrials.gov](https://clinicaltrials.gov) identifier NCT02503800).

A total of 159 individuals were enrolled (Table I), with a median age of 18 years (range, 3-75 years) at the onset of VIT and a female to male ratio of 1:3.5. Most of the subjects were sensitized to honey bee venom (88.7%) followed by yellow jacket (22.6%) and wasp (10.7%) venoms. A rush VIT buildup protocol was used in 93.1% of the cases, as previously described,⁴ and nearly all of the patients (96.9%) reached the full maintenance dose of 100 mcg venom. Pretreatment intake interviews disclosed near-fatal reactions in 27 patients (17%). Throughout treatment, 43 participants (27%) experienced a systemic reaction during the buildup phase, whereas 15 (9.4%) reacted to the maintenance doses.

In terms of MC markers, the average BTC level was 5.6 ng/mL, with 6 individuals (3.8%) exceeding the upper limit of the normal range (11.4 ng/mL). Four of the 96 subjects (4.2%) who were tested for the D816V c-Kit mutation in peripheral blood were found positive.

Patients who had experienced near-fatal reactions to stings differed from those with less severe reactions by their higher BTC (7.1 vs 5.3 ng/mL; $P = .03$) and older age at the onset of therapy (44 vs 17 years; $P < .0001$). Subjects who experienced reactions to treatment during the buildup phase showed no difference from those who did not react in BTC, age, and history of near fatal stings. However, sensitization to bee venom was significantly more prevalent among individuals who experienced adverse events (90.7% vs 69%; $P = .004$). None of the 43 subjects who experienced an allergic reaction to VIT had life-threatening events.

Our study revealed 7 individuals with at least 1 abnormal MC-associated finding (Table II). Of the 6 patients with elevated BTC (>11.4 ng/mL), 3 had the c-Kit D816V mutation in peripheral blood. Another carrier of the c-Kit mutation had a normal BTC value (4.8 ng/mL). Two subjects with abnormal BTC and c-Kit mutation along with adverse reactions to VIT were referred for a bone marrow biopsy, one of whom was diagnosed with SM. This was the only patient with abnormal biomarkers who had experienced a life-threatening allergic response to field sting. Although 3 subjects had adverse events during VIT, all 7 individuals reached the full maintenance venom dose of 100 mcg.

In this study, we have obtained peripheral blood MC biomarkers from an Israeli cohort of patients with HVA. The data presented herein exhibit several differences compared with previous reports from Europe. Our study population displayed a median age of 18 years, in contrast to median ages in the 30s to 50s, as previously reported.^{2,5-7} We hypothesize that the young patient-age may be due to early exposure to insects, resulting from a relatively warm climate combined with a local lifestyle of spending outdoor time at young ages. The proportion of patients with HVA who have elevated tryptase values (>11.4 ng/mL) has been reported to be 10% to 15.9%.⁸ The

TABLE I. Population characteristics

Subjects, N	159
Age*, years, median (range)	18 (3-75)
Female/male ratio	1/3.5
Sensitizing venom, N (%)	
Bee	141 (88.7)
Yellow jacket	36 (22.6)
Wasp	17 (10.7)
Rush immunotherapy protocol, N (%)	148 (93.1)
Full maintenance dose, N (%)	154 (96.9)
Near fatal sting reactions, N [†] (%)	27 (17)
Reactions to buildup, N (%)	43 (27)
Reactions to maintenance, N (%)	15 (9.4)
Tryptase, ng/mL, mean (SD) (N = 157)	5.6 (3.9)
Tryptase value >11.4 ng/mL, N (%)	6 (3.8)
c-Kit mutation, N (% of 96): positive	4 (4.2)

*At onset of immunotherapy.

†Grading of anaphylaxis severity: (1) mild (skin and subcutaneous tissue only); (2) moderate (features suggesting respiratory, cardiovascular, or gastrointestinal involvement); (3) near fatal (hypoxia, hypotension, or neurologic compromise).

In conclusion, we present a single-center experience of Israeli HVA patients, who are considerably young, and discloses a high rate of bee venom sensitivity. The number of subjects with abnormal MC biomarkers is remarkably lower than previously published. We conclude that population and geographical variability may require corresponding adjustments in risk factor interpretation.

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TABLE II. Patients with Abnormal Peripheral-Blood Mast Cell Markers

Age/sex	Reaction to sting	Venom type	Reactions to therapy (buildup/maintenance)	c-Kit D816V	Tryptase (ng/mL)	Full maintenance dose	Comments
14/M	Moderate	Bee	No/No	Positive	4.8	Yes	
15/M	Moderate	Bee	No/No	Negative	14.5	Yes	
18/M	Moderate	Bee; YJ	No/No	Negative	12.9	Yes	
32/F	Moderate	Bee	Yes/Yes	Positive	16.9	Yes	Normal bone marrow
33/M	Moderate	Bee	Yes/No	Positive	17.9	Yes	
61/M	Moderate	Bee	No/No	Negative	11.5	Yes	
71/F	Near fatal	Bee	Yes/Yes	Positive	41.9	Yes	SM in bone marrow

SM, Systemic mastocytosis; YJ, yellow jacket.

actual number in this study was 6 patients (3.8%), similar to the range of 4% to 6%, which was reported for the general population.⁹ This difference may be hypothetically explained by young age, ethnic background, or low susceptibility to mast cell disorders. We conclude that screening of patients for such biomarkers has a limited effect on management of HVA in this specific population. This is in contrast to previous studies where the rate of severe reactions was considerably higher in individuals with high BTC (>11.4 ng/mL). Therefore, we suggest that it is more effective to seek mastocytosis by clinical evaluation for severe reactions or adverse events during VIT rather than universal laboratory screening. In comparison with vespids, bee venom allergy has been shown to be less affected by BTC, and its preponderance in our work (89% vs 20%-30% in European series) may account, in part, for the limited clinical effect of excessive tryptase values.

Our study is limited by the fact that the results were derived from a single hospital. This fact entails a potential referral bias of patients who represent the local population. Another limitation is that we did not include parameters of primary MC disorders such as bone marrow biopsy (with the exception of 2 subjects) and duplication of the α -tryptase encoding gene.⁹ Therefore, underestimation of MC abnormalities is possible.

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