

Natural history of Hymenoptera venom allergy in children not treated with immunotherapy



Joanna Lange, MD, PhD^{*}; Ewa Cichocka-Jarosz, MD, PhD[†]; Honorata Marczak, MD^{*}; Agnieszka Krauze, MD, PhD^{*}; Izabela Tarczoń, MD[†]; Ewa Świebocka, MD, PhD[‡]; Grzegorz Lis, MD, PhD[‡]; Piotr Brzyski, PhD[§]; Anna Nowak-Węgrzyn, MD, PhD^{||}

^{*} Department of Pediatric Pneumonology and Allergy, Medical University, Warsaw, Poland

[†] Department of Pulmonology, Allergy, Dermatology, Jagiellonian University Medical College Kraków, Poland

[‡] Department of Pediatrics, Children's Gastroenterology and Allergology, Medical University, Białystok, Poland

[§] Department of Medical Sociology, Chair of Epidemiology and Preventive Medicine, Jagiellonian University Medical College, Kraków, Poland

^{||} Icahn School of Medicine at Mount Sinai, Jaffe Food Allergy Institute, New York, New York

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ABSTRACT

Background: Differences in treatment approach still exist for children after systemic sting reactions. In addition, there are still some doubts about when systemic reactors should be treated with venom immunotherapy (VIT).

Objective: To determine the rate of sting recurrence and natural history of Hymenoptera venom allergy (HVA) in children not treated with VIT.

Methods: A total of 219 children diagnosed as having HVA who were not treated with VIT were identified in 3 pediatric allergology centers. Survey by telephone or mail with the use of a standardized questionnaire was conducted. The number of field re-stings, subsequent symptoms, and provided treatment were analyzed.

Results: A total of 130 of the 219 patients responded to the survey, for a response rate of 59.4%. During the median follow-up period of 72 months (interquartile range, 52–85 months), 44 children (77% boys) were stung 62 times. Normal reactions were most common, occurring in 27 patients (62%). Severe systemic reactions (SSRs) occurred in 8 (18%) of those who were re-stung. The subsequent reaction was significantly milder ($P < 0.001$), especially in the case of patients re-stung by the same insect ($P < .001$). None of the children with prediagnostic large local reactions and negative test results for venom specific IgE developed SSRs after re-sting by the culprit insect ($P = .03$). In children with SSRs, median time from diagnosis to re-sting was 2 times longer than that in those with large local reactions and normal reactions ($P = .007$).

Conclusions: Most children with HVA not treated with VIT reported milder reactions after a re-sting. Probability of SSR to re-sting increases along with the severity of initial reaction.

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Introduction

Hymenoptera venoms are among the top causes of anaphylaxis in adults and children in Europe and North America.^{1–4} Hymenoptera venom allergy (HVA) with respiratory and/or cardiovascular symptoms is a serious, potentially life-threatening condition that is mostly commonly found in adult populations. The decision to start venom immunotherapy (VIT) is based on a history of a systemic IgE-mediated allergic reaction mechanism according to the European Academy of Allergy and Clinical Immunology (EAACI) and US guidelines (Table 1).^{5,6}

Reprints: Joanna Lange, MD, PhD, Department of Pediatric Pneumonology and Allergy, Żwirki i Wigury 63A, 02-091 Warsaw, Poland; E-mail: joanna_lange@wp.pl.

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Treatment is highly effective, with an efficacy of up to 98% in children.⁷ VIT is not indicated for large local reactions, whereas it may be considered in mild sting-induced systemic reactions (SRs), especially in the presence of comorbidities. Children usually develop mild reactions to stings, but a substantial number of severe reactors, who do not outgrow the HVA, remain at high risk (30%–40%) for life-threatening reactions even after 10 to 20 years.⁸ Only a few articles have discussed the natural course of HVA. Data exploring this issue in pediatric populations are still scarce.^{8–11} We undertook a multicenter, retrospective study to investigate the natural history of HVA in children not treated with VIT with special emphasis on mild systemic reactors. The aim of the study was to examine the rate of re-sting and severity of clinical reactions after re-sting.

Table 1
Indication for VIT According to European/US Guidelines⁵⁶

Type reaction (adults/children)	Diagnostic tests (skin test and/or specific IgE)	Indication for VIT
Respiratory and/or cardiovascular symptoms of Mueller grades III and IV		
Adults/children	Positive	Yes
	Negative	No
Urticaria/edema of Mueller grades I and II if risk factors or QoL impairment present		
Adults/children	Positive	Yes
	Negative	No
Large local	Positive or negative	Usually no ^a
Unusual reaction	Positive or negative	No

Abbreviations: sIgE, specific IgE; QoL, quality of life; VIT, venom immunotherapy.
^aPatients with frequent and unavoidable stings resulting in repeated large local reactions may benefit from VIT.

Methods

Study Population

Patients available for the study were selected from the data-bases of 3 pediatric allergology departments in Poland, where their conditions were diagnosed after Hymenoptera sting reaction between 2003 and 2012. The study population comprised children who fulfilled at least 1 of the following inclusion criteria: (1) lack of clinical and immunologic indications for VIT⁶; (2) contraindication to VIT at the time of diagnosis based on EAACI guidelines, such as autoimmune disease, especially in unstable stage, neoplasm, or severe systemic disease⁶; and/or (3) lack of written consent from patients 16 years or older or from the parents of patients younger than 16 years, despite medical indications for immunotherapy. In total, 219 children (mean age, 10.9 years; range, 3–18 years; 148 boys) were eligible for the questionnaire study (Krakow, 114; Warsaw, 81; Bialystok, 24). Informed consent from the study participants was obtained orally. Most of the eligible children did not meet the criteria for the VIT (Fig 1).

Diagnostic Data

Baseline data included a detailed history of the insect sting event, evaluation of the severity of the insect sting reaction, and medical intervention based on the original medical records. Diagnostic procedures, according to EAACI recommendations, were performed with a specific IgE evaluation via skin tests and blood sample analysis.¹² Skin prick tests and intradermal tests with venom extract (HAL Allergy B.V., Leiden, the Netherlands, or Pharmedica ALK-Abello, Hørsholm, Denmark) (*Apis mellifera* and

Vespula spp) were performed, and the results interpreted according to the EAACI guidelines.¹² Venom specific IgE antibodies were analyzed by the IgE immunoassay (Immuno-CAP, Pharmacia Diagnostic, Uppsala, Sweden), according to the manufacturer's recommendations. A positive result was defined as greater than 0.35 kU/L (class ≥ 1).

Survey Questionnaire

Data were collected using a standardized questionnaire composed of questions related to the time and number of field re-stings, type of stinging insect, subsequent symptoms, treatments (physician's intervention, including oral and parenteral drugs and hospitalization), and atopic disorders (asthma, allergic rhinitis). Institutional review board approval was not required for this study.

Evaluation of the Severity of Reaction

Both prediagnostic and follow-up (re-sting) clinical reactions were graded as follows: (1) normal reactions (NRs), which were applicable only to follow-up period stings defined as swelling less than 10 cm in diameter lasting less than 24 hours; (2) large local reactions (LLRs), which were defined as swelling greater than 10 cm in diameter or lasting for more than 24 hours; (3) SRs, which were classified according to the Mueller's scale as mild systemic reactions (MSRs), including grades I and II, and severe systemic reactions (SSRs), including grades III and IV^{12,13}; or (4) unclassified reactions (UCRs), which entailed all symptomatic reactions that could not be classified according to the Mueller's scale, such as vomiting, fever, localized skin pruritus, or subjective symptoms (eg, only one parameter, such as prickling of the tongue or dizziness).¹³

Follow-up Evaluation

The study was conducted in January 2014. Eligible participants were contacted primarily via telephone. For the individuals without telephone contact, a questionnaire was mailed to the home address on file.

Statistical Analysis

Data were reported as proportion, mean (SD), or median (interquartile range [IQR]), as appropriate. The nonparametric χ^2 , Mann-Whitney, and marginal homogeneity tests were used. $P < .05$ was considered statistically significant. All the statistical analyses were performed using SPSS statistical software for Windows, version 22 (SPSS Inc, Chicago, IL).

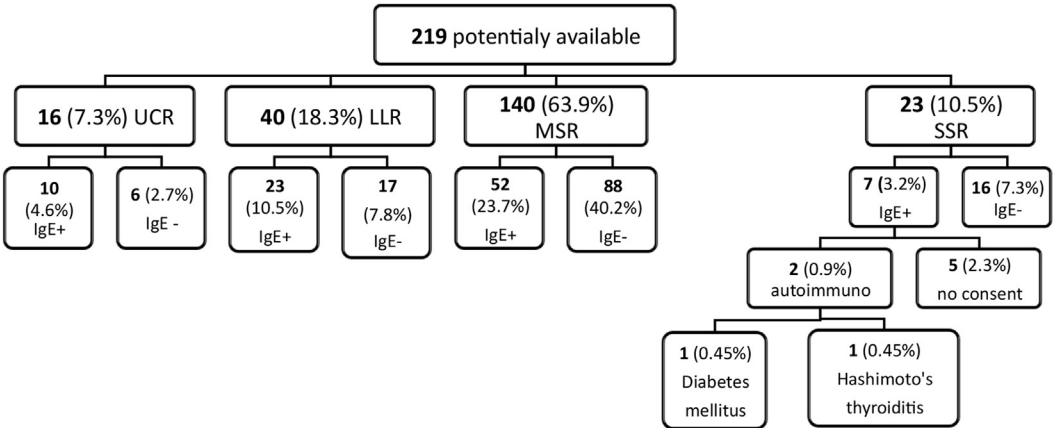


Figure 1. Indications for deferral of venom immunotherapy (VIT). LLR, large local reaction; MSR, mild systemic reaction; SSR, severe systemic reaction; UCR, unclassified reaction.

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