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Simplification of intradermal skin testing in Hymenoptera venom allergic children

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ABSTRACT

Background: The direct comparison between children and adults with Hymenoptera venom anaphylaxis (HVA) has never been extensively reported. Severe HVA with IgE-documented mechanism is the recommendation for venom immunotherapy, regardless of age.
Objective: To determine the differences in the basic diagnostic profile between children and adults with severe HVA and its practical implications.
Methods: We reviewed the medical records of 91 children and 121 adults.
Results: Bee venom allergy was exposure dependent, regardless of age ($P < .001$). Atopy was more common in children ($P = .01$), whereas cardiovascular comorbidities were present almost exclusively in adults ($P = .001$). In the bee venom allergic group, specific IgE levels were significantly higher in children (29.5 kU_A/L; interquartile range, 11.30-66.30 kU_A/L) compared with adults (5.10 kU_A/L; interquartile range, 2.03−8.30 kU_A/L) ($P < .001$). Specific IgE levels for culprit insect venom were higher in bee venom allergic children compared with the wasp venom allergic children ($P < .001$). In adults, intradermal tests revealed higher sensitivity, accompanied by larger area of skin reactions, regardless of type of venom. At concentrations lower than 0.1 μg/mL, 16% of wasp venom allergic children and 39% of bee venom allergic children had positive intradermal test results. The median tryptase level was significantly higher in adults than in children for the entire study group ($P = .002$), as well as in bee ($P = .002$) and wasp venom allergic groups ($P = .049$).
Conclusions: The basic diagnostic profile in severe HVA reactors is age dependent. Lower skin test reactivity to culprit venom in children may have practical application in starting the intradermal test procedure with higher venom concentrations.

Introduction

Hymenoptera venom allergy (HVA) caused by Vespinae and *Apis mellifera* has different characteristics in children and adults; however, direct comparisons between severe reactors in these groups of patients have not been extensively explored. Epidemiologic studies on HVA originating from the United States in the early 1970s reported that in the scout subpopulation the prevalence of insect sting allergy was low (0.3%−0.4%).[1,2] Similar data, ranging from 0.2% to 0.8%, were reported from European children,[3–5] whereas data from Israel estimate HVA at 9%.[6] Among US adults, according to the studies by Golden et al[7,8] from the 1980s, the prevalence of systemic reactions (SRs) was estimated at approximately 3%. More recent European epidemiologic studies of the general population reported a prevalence of SRs between 1.5% and 8.9%.[4] The European Anaphylaxis Registry confirmed that venom accounts for 40% of known elicitors of anaphylaxis in teenagers aged 13 to 17 years and 36% in children aged 6 to 12 years.[9,10] In adults, the rate of hospital admissions increased since the early 1990s, but the annual fatality rate remained stable, with the highest risk reported in male adults older than 60 years.[11,12] Similar data were reported by Graft[13] from

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the United States, where the number of deaths was usually the highest in age groups from 50 to 69 years. Male deaths outnumbered female deaths. In the United States, the total number of deaths caused by insect stings was stable from 1980 to 1999.

In contrast, pediatric hospitalizations for HVA peaked at the mean (SD) age of 7.6 (3.2 years),[12,14] and no fatalities were reported within the past 2 decades.[11,12,14,15] Approximately a quarter of fatalities from anaphylaxis are triggered by venom allergy.[11,12] In both age groups, mortality rates might be underestimated. Despite geographic differences, HVA is clinically important in both Europe[9,10] and North America.[16]

The 4-degree clinical classification of anaphylactic reactions severity is frequently used for the evaluation of SRs to insect stings.[17] In children, milder reactions and better recovery are expected because of a healthy cardiovascular system, unimpaired by age-related disorders, including mastocytosis and cardiovascular medications. Almost 50% of children and adults had respiratory symptoms, whereas 60% have hypotension and 30% loss of consciousness. Cardiovascular symptoms in adults highly outnumbered their prevalence in children.[18] Likewise, in a study from the 1980s, hypotension was rare in children, whereas respiratory symptoms were as common in children as in adults. Cutaneous SRs were more common in children.[19] The same authors also reported the predominance of honey bee venom allergy in children.[19]

Children with severe HVA have a 40% risk of a severe reaction to a subsequent sting within the first decade after a severe reaction and 30% within the second decade compared with a comparative risks of 60% and 40% in adults.[20] Similar data were reported by Reisman et al[21] regarding the likelihood of subsequent reactions at re-sting in patients with a history of severe cardiovascular and/or respiratory symptoms due to a previous sting, although age was not a major factor in predicting SRs on re-sting. In another study by Reisman,[22] among 220 patients with HVA not treated with venom immunotherapy (VIT), the incidence of a reaction after the first re-sting was more frequent in adults (74%) than in children (40%) and was unrelated to the interval since the initial sting reaction. In a study by Lange et al,[23] although most children with HVA not treated with VIT reported milder reactions after a re-sting, severe SRs occurred in 18%.

Severe HVA is an indication for VIT as per international guidelines, regardless of age.[24–27] VIT is the only causal treatment of HVA, which prevents severe future SRs and improves patient's quality of life.[28] Before initiating VIT, IgE-dependent HVA needs to be confirmed by skin testing and/or serum sIgE measurement.[24,25,27] Currently, available tests do not reliably distinguish between asymptomatic and symptomatic sensitization to insect venom.

Despite the first comparison of severe reactors dating back 30 years,[18] today comprehensive studies directly between children and adults with severe HVA continue to be scarce. Diagnostic profile and response to VIT are much better characterized in adults than in children.[28,29] Even when the study sample includes both age groups, the results are averaged or age is not a discriminant factor for the analysis.[30–33] Starting in 1999, international guidelines for HVA management have been issued and periodically updated. These guidelines are identical for children and adults with severe HVA.[17,27] We sought to evaluate the differences in clinical and laboratory characteristics of HVA in children compared with adults and to determine whether they have clinical implications for management.

Methods

We analyzed medical records of all children and adults with the history of systemic grade III to IV reactions treated with single VIT in 2 university-affiliated (tertiary-level) allergy centers in Krakow, Poland, from 2007 to 2014. We identified 215 severe reactions from Southeastern Poland. In all patients, IgE sensitization to Hymenoptera venom was confirmed; 3 patients (1 adult and 2 children) sensitized to both honeybee and wasp venoms were excluded from the analysis. Ultimately, data of 121 adults (≥18 years old) and 91 children (3–17 years old) with single venom allergy was analyzed. Demographic and clinical characteristics of the study population are given in Table 1. All procedures were approved by the Jagiellonian University Ethical Committee.

Table 1
Characteristics of the Study Population[a]

Characteristic	Adults (n = 121)	Children (n = 91)	*P* value
Male	64 (53)	69 (76)	.001
Age, mean (SD) [range], y	39.7 (13.8) [18–70]	10.9 (4.1) [3–17]	<.001
Rural area residence	76 (63)	63 (69)	NS
Atopy	22 (18)	30 (34)	.01
Asthma	25 (21)	8 (9)	.02
Mastocytosis	5 (4)	0 (0)	.07
Hypertension	21 (18)	0 (0)	<.001
Ischemic heart disease	10 (9)	0 (0)	.006
Thyroid diseases	9 (8)	0 (0)	.01
Ventricular septal defect	0 (0)	1 (1)	NS

Abbreviation: NS, nonsignificant.
[a]Data are presented as number (percentage) of patients unless otherwise indicated.

The culprit insects reported in this article are honeybee (*Apis mellifera*) and wasp (*Vespula*). Because hornet's venom extract is not available in Poland, neither for diagnostic nor for treatment purposes, the patients who were stung by *Vespa crabro* were evaluated with wasp venom extract and were classified in this article as sensitized to wasp venom.

The following information of both standard diagnostic procedures and safety aspects was collected and coded in the same way for all children and adults. A detailed medical history of SRs to insect sting was taken. Severity of HVA was graded according to the European Academy of Allergy and Clinical Immunology (EAACI) guidelines (grade III, dyspnea, wheezing, stridor, dysarthria, hoarseness, weakness, confusion, feeling of impending doom; and grade IV: decrease in blood pressure, collapse, loss of consciousness, incontinence, and cyanosis).[17] Medical history of comorbidities, including asthma, atopy, mastocytosis, circulatory diseases, and cardiac pharmacotherapy, was elicited. The examination of the skin was performed to detect mastocytosis. Laboratory diagnostic tests were performed, including the following blood tests: serum wasp and honeybee venom specific IgE (sIgE) determinations for wasp venom and honeybee venom allergens with a threshold for positivity of 0.35 kU_A/L or higher and baseline serum tryptase (bsT). Both tests were performed by fluoroenzyme immunoassay using a UniCAP 100 immunology analyzer (CAP System, Phadia, Uppsala, Sweden). Intradermal tests (IDTs) were performed by an allergy nurse specialist (2 in each center) according to the same protocol in children and adults.[24] Briefly, 0.02 mL of aqueous venom extracts at concentrations of 0.0001, 0.001, 0.01, 0.1, and 1.0 μg/mL were given intradermally as per standard protocol (Pharmalgen, ALK Abello, Hørsholm, Denmark).[34] Test results were interpreted as positive when after 20 minutes the wheal diameters were equal or greater than 5 mm. Skin prick tests (SPTs) were performed as per standard protocol with a standard panel of aeroallergens (Nexter Allergopharma, Darmstadt, Germany) in all participants.[34] In case the insect was not identified, IDTs with venom extract of the other kind of insect were performed 3 to 6 weeks later, according to the EAACI guideline recommendations with intervals of 1 to 2 months.[17] bsT determination, atopy-verifying tests, and pulmonary function tests were performed 1 day before initiation of VIT. Data on systemic adverse effects during skin testing were collected.