

Research Article

# Higher venom-specific IgE levels differentiate children with previous local large reactions from children with previous systemic reactions of different severity

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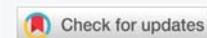
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**Keywords:** Hymenoptera venom; Large local reactions; Systemic reactions; Specific venom IgE; Children



## Abstract

**Introduction:** Risk factors for systemic reactions (SRs) from hymenoptera venom (HV) allergy are well known in the adult population but they have been little studied in the pediatric one.

**Method:** The aim of our study was to identify risk factors for SRs in a population of children allergic to HV, comparing a series of clinical (age, gender, atopy, asthma) and laboratory (total IgE, tryptase, venom-specific IgE levels) variables between patients with at least two large local reactions (LLRs) and patients with SRs of different severity for the identified insect. We selected a population of HV allergic children aged < 15 years with LLRs or SRs stratified according to Mueller grades after stinging.

**Results:** The population included 80 children, 35 with at least 2 LLRs and 45 with SRs. The level of specific IgE for vespid (*Polistes dominula*, *Vespa species*) venoms was significantly higher ( $p = 0.0321$ ) in children with SRs (Mueller grade II+III+IV) than in those with LLRs and the same significance was also found for specific IgE for *Apis mellifera*, considering SRs group (Mueller grade I+II+III+IV) in respect with LLRs group ( $p = 0.0001$ ).

**Conclusion:** The main difference in our pediatric population was the highest level of specific IgE in children with a history of SRs compared to those with a history of LLRs for both vespids and honey bees. These results, once confirmed on a larger population, could suggest the opportunity to follow the behavior of venom specific IgE in children with LLRs to reveal a risk to develop future more serious reactions.

## Introduction

Anaphylaxis in children is a relatively rare event, but in the last 20 years, based on both the number of hospitalizations and the number of fatal anaphylaxis, a significant increase has been observed [1]. With regards to allergic reactions to hymenoptera venom, however Turner, et al. showed stability

over time both in the number of hospitalizations and in the number of fatal events [2]. On the other hand, hymenoptera venom rarely causes severe and/or fatal anaphylactic episodes in the pediatric setting [3].

However, it is an epidemiologically important cause of systemic allergic reactions in children, so much so

that according to the European Anaphylaxis Registry [4], 19% out of 1970 subjects aged < 18 years experienced an anaphylaxis episode from allergy to hymenoptera venom, found to be the second most frequent cause of anaphylaxis in a pediatric population consisting of children and adolescents. Unlike in adults, reactions to hymenoptera venom tend to spontaneously improve especially in subjects < 16 years of age with only skin reactions, even if generalized; for this reason the guidelines suggest not to undertake diagnostic tests or Specific Immunotherapy (ITS) in this population [5,6].

Severe systemic reactions in the general pediatric population appear to be rarer than in adults [7], with a prevalence < 1% [8]. However, considering a recent study carried out on a group of children selected for systemic reactions to hymenoptera venom, Yavuz, et al. [9] found a rate of severe reactions (Mueller grade III + IV) equal to 59%.

The majority of risk factors for severe systemic reactions in the adult population are known from the literature, while they have been little studied in children. Graif, et al. in 2009 have identified atopy as a risk factor while Yavuz, et al. in 2013 identified moderate eosinophilia, female sex and atopy [9,10].

The aim of our work was to identify the risk factors for severe systemic reactions in a population of subjects aged < 15 years allergic to hymenoptera venom. For this purpose, age, gender, atopy, asthma, tryptase, total IgE and venom specific IgE antibodies (Abs) levels for the different hymenoptera venoms were compared between a population of children with large local reactions (LLRs) and a population of children with systemic reactions (SRs).

## Materials and methods

### Patients

Pediatric subjects (< 15 years old) consecutively referred to the Allergy and Immunology Unit of the Niguarda Ca' Granda Hospital (Milan, Italy) for a documented history of allergic reactions to Hymenoptera venom (HVA), were retrospectively studied. All the children have been diagnosed according to the guidelines [8].

The study population included children with a history of at least two LLRs given the low risk of a subsequent SR and children with documented SRs to Hymenoptera stings both for the identified insect [11]. Large local reaction was characterized by oedema, erythema or itch with an area of oedema > 10 cm of diameter and a peak between 24 to 48 hours [12]. Systemic reactions were graded into four classes according to Mueller's classification (grades of severity I–IV) [13].

For each patient, the following data were collected: age, gender, atopy (presence of positive IgE against one or more inhalant allergens and a history of asthma and/or rhinitis and/or atopic dermatitis), history of bronchial asthma (following

GINA: <https://ginasthma.org>), total serum IgE (value sensitization > 100 kU/L; ImmunoCAP System Thermo Fisher Scientific), venom specific IgE for *Apis mellifera*, *Vespula spp.*, *Polistes dominula*, (positive value > 0.10 kUA/L; ImmunoCAP System Thermo Fisher Scientific) and basal serum tryptase value (sBT) (normal range < 11.4 ng/mL; ImmunoCAP System Thermo Fisher Scientific). The primary end point of the study was the comparison of all these data between the groups of children with previous SRs versus the ones with previous LLRs. Given the low positive number of patient allergic to *Polistes dominula* for the statistical analysis the laboratory data were combined with those of the *Vespula spp.* For each patient an attempt was made to identify the insect responsible for both LLRs and SRs by distinguishing in particular between vespid and honey bee.

The study protocol was approved by the Ethics Committee of ASST Grande Ospedale Metropolitano Niguarda (Milan, Italy) on October 26<sup>th</sup> 2018, protocol ID 538-102018.

### Statistical analysis

All the collected data were validated before submission to usual descriptive statistics: categorical binary, nominal and ordinal variables were given as relative and absolute frequency tables, while continuous variables were described with mean and standard deviation or with median and range, depending on their distribution, which was checked with visual inspection of the histogram, as well as by the Shapiro-Wilk test.

Cross-tabulations of the categorical variables were analysed with Fisher's exact test. The effects exerted by continuous or categorical non-binary variables on binary dependent variables were analysed using the logistic regression with Wald's test, whereas the differences between continuous variables have been evaluated by two-sided/two-tailed Student's t test, or by Welch's test, or by the Mann-Whitney U test with exact algorithm, depending on variable distribution and on variance homogeneity.

## Results

### Patients

The study population included 80 children (58 males and 22 females, median age 10 years, range 4-15 years), of whom 35/80 with previous LLRs (43.75%, 26 males and 9 females, median age 10 years, range 5-14 years) and 45/80 (56.25%; 32 males and 13 females, median age 9 years, range 4-15 years) with a history of SRs. Amongst the 45 children with SRs, 22/45 (48.89%) were classified as Mueller grade I, 9/45 (20%) as grade II, 12/45 (26.66%) as grade III, and 2/45 (4.44%) as grade IV. Stratifying for the stinging insect, we observed that for vespids 14/27 (51.85%) patients presented a Mueller I reaction, 8/27 (29.63%) a Mueller II, and 4/27 (14.81%) a Mueller III and 1/27 (3.70%) a Mueller IV reaction, while for bee venom 8/18 (44.44%) patients presented a Mueller I

reaction, 1/18 (5.55%) a Mueller II, 8/18 (44.44%) a Mueller III, and 1/18 (5.55%) a Mueller IV reaction. A summary of patient's demographic, clinical and laboratory data are shown in table 1.

Comparison of the various clinical and immunological parameters between patients with LLRs and SRs.

By comparing all considered variables, we did not find any statistical difference between LLRs and SRs patients as regards to age, gender, atopy, asthma, tryptase levels (ng/mL), and serum total IgE (kUA/L), with values reported in table 1.

Conversely, a statistically significant association was found between the severity of the reaction and venom-specific IgE levels for vespids and *Apis mellifera*. In fact, children with SRs (Mueller grade II+III+IV) for vespid venom presented a significantly higher levels of vespid specific IgE than children with vespids-induced LLRs; similarly children with SRs (Mueller I+II+III+IV) for *Apis mellifera* venom presented higher levels of honey bee specific IgE than children with honey bee-induced LLRs (Mann-Whitney exact test:  $p = 0.0321$  and  $p = 0.0001$  respectively) (Figures 1,2).

In other words these results showed that there is a 73.1% chance that a child with SRs compared to a child with LLRs had higher specific IgE Abs levels against Vespids and 87.0% chance against *Apis mellifera*.

## Discussion

In this work, we analyzed the risk factors for severe anaphylactic reactions from hymenoptera venom allergy in a pediatric population with previous documented reactions to these insects. For this purpose, we compared a series of clinical and biological parameters between a group of 35 children who had previously presented at least two LLRs and one of 45 children who had presented systemic reactions of varying severity. It should be noted that in the group of children with systemic reactions we identified two subjects with a reaction classifiable as Mueller IV because they had presented a cardiovascular collapse, associated with very brief loss of consciousness, whereas 26.6% of the children we evaluated for severe systemic reaction reported a clinical

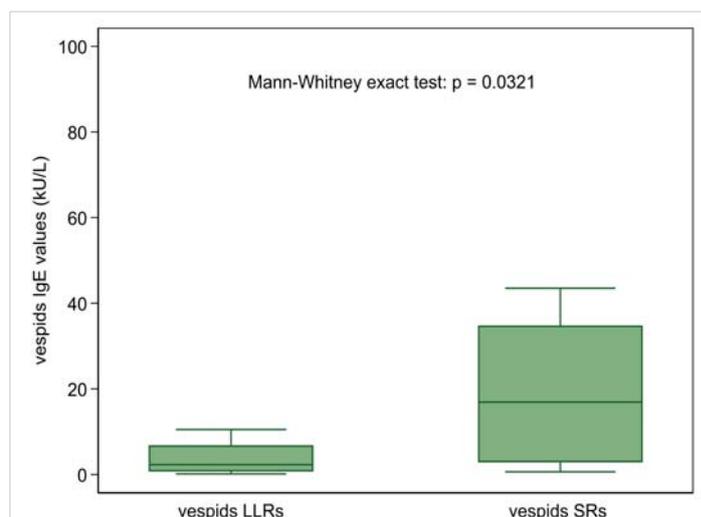


Figure 1: Vespid IgE specific values in LLRs patients and in SRs patients allergic to vespid venom.

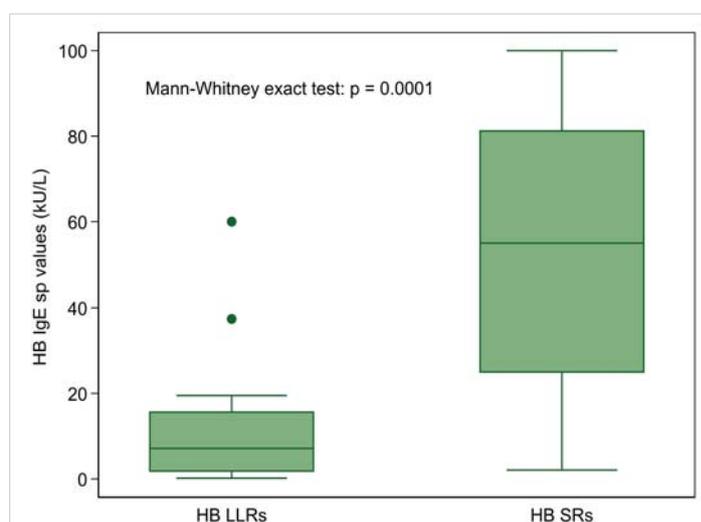


Figure 2: HB (honey bee) IgE specific values in LLRs patients and in SRs patients allergic to HB venom.

picture definable as Mueller III. The finding of a low prevalence of severe anaphylactic reactions in our case series confirms previous data from the literature [7], since it is known that HVA in children causes mainly skin reactions and is less severe than in adults [8]. Similarly, more recently in the case series of Blum, et al. [14], including adults and children, the group

Table 1: Patient's demographic, clinical and laboratory data.

	Total	SRs	LLRs	p value
Patients	80	45/80 (56.25%)	35/80 (43.75%)	
Gender (M/F)	58/22	32/13	26/9	0.805*
Median Age, (min-max)	10 (4-15)	9 (4-15)	10 (5-14)	0.3653**
Atopy	28/80 (35%)	13/45 (28.8%)	15/35 (42.8%)	0.240*
Anti-Vespid IgE levels kU/L median value, (min-max)	n.c.	4.26 (0.38-100)	2.29 (0.14-100)	0.0321**
Anti- <i>Apis mellifera</i> IgE levels kU/L median value, (min-max)	n.c.	55.0 (2.06-100)	7.13 (0.17-60)	0.0001**
sBT levels ng/mL median value, (min-max)	n.c.	3.3 (1.1-13.4)	3.2 (1.8-8.5)	0.7470**
Total IgE kUA/L median value, (min-max)	n.c.	347.5 (29.3-3418)	253.5 (12-2770)	0.1137**

M: Male; F: Female; LLRs: Local Large Reactions; SRs: Systemic Reactions; sBT: serum Basal Tryptase; \*Fisher's exact test; \*\*Mann-Whitney test with exact algorithm; n.c.: not calculate



of children/adolescents showed few severe anaphylaxis and mostly reactions classifiable as Mueller III. The two groups of children studied were then compared with each other with regard to the prevalence of gender, atopy, allergic diseases in general and asthma in particular as well as levels of tryptase, venom-specific and total IgE Abs.

In some cases the IgE values were clearly positive for both honey bee and vespids venoms but with very different levels and with a clear clinical identification of the culprit stinging insect on the basis of history and positivity of skin tests and the major allergens (when tested).

Considering the SRs of all severities compared to the LLRs, we found that the only difference that significantly distinguished the two populations of children was represented by the level of venom-specific IgE Abs. This result is noteworthy because it was confirmed for both vespid and *Apis mellifera* venoms, thus demonstrating that as the concentration of venom-specific IgE increased, the clinical reactivity increased too, ranging from a simple large local reaction to systemic reactions of various severity. As a matter of fact, in our work a difference in venom-specific IgE Abs was identified between LLRs and mild to severe SRs (Mueller I+II+III+IV) for *Apis mellifera* and between LLRs and moderate to severe SRs (Mueller II+III+IV) for vespids.

These specific differences would indicate that the severity of the allergic reaction is closely dependent on the level of venom-specific IgE Abs. Few studies have so far demonstrated a relationship between venom-specific IgE Abs level and the severity of the reaction in children, and particularly between those present in LLRs and moderate and severe SRs [15]. On the other hand, this absence of correlation between IgE level and severity has been well demonstrated especially for the adult population in which the dissociation of the two phenomena is more evident with increasing age [16]. In the older population, an inverse correlation has even been demonstrated, i.e. lower levels of venom-specific IgE Abs correspond to more severe reactions. In adults, in fact, the severity of the reaction is more than anything else conditioned by problems of clinical relevance, as we have recently demonstrated, confirming previous studies [17]. For example, many authors have identified the presence of hypertension or various types of cardiovascular diseases as the main risk factors for severe anaphylactic reactions [18]. Moreover, in adults the presence of Mastocytosis or in any case of an elevated level of tryptase in basal condition has been identified as factors favoring severe SRs [19]. In children in our population, tryptase levels were found to be superimposable between the 2 considered groups of LLRs with respect to both moderate and severe SRs. We also did not identify pediatric subjects in our study population with either cutaneous or systemic Mastocytosis. Therefore, it does not appear that a clonal mast cell disease is involved in the severity of the anaphylactic reaction to hymenoptera venom in children.

Nor was a distinctive role of atopy or of the prevalence of atopic diseases such as asthma or rhinitis in distinguishing populations of different severity confirmed in the children we studied. However, it should be considered that in our population, considered as a whole of 80 children, the prevalence of atopy was 35%, thus similar to that of the general population. We can't therefore confirm the data from the literature that would have shown a higher prevalence of allergy to hymenoptera venom in the population of atopic subjects than in non-atopic ones [9,10]. However, atopy did not differentiate LLRs from severe SRs.

Moreover, also Solley, et al. [20] in 2004, in an Australian study, did not find any statistical association between the presence of atopic diseases and severe systemic reactions. These results differ from those of Graif, et al. [10] who in 2009 identified atopy and asthma as risk factors for severe anaphylactic reactions from hymenoptera venom in a population of 14,306 boys aged between 13 and 14 years. However, this comparison was carried out with the general population and not with subjects with LLRs.

We also found no gender difference between patients with LLRs or with systemic reactions unlike Yavuz, et al. [9] who in 2013, studying a population of 76 children with a mean age of 9.8 years and systemic reactions, identified, as risk factors for severe anaphylaxis, the presence of moderate eosinophilia and female sex as well as atopy.

Another unconfirmed data in our pediatric population but actually described in the literature only in adults, and especially in the elderly adult, was the correlation between low total IgE levels and a high probability of loss of consciousness or in any case of Mueller IV [21]. In the population of children we described there was only one grade IV reaction with loss of consciousness and the total IgE showed no difference between children with Mueller grade III + IV reactions and those with LLRs.

To distinguish the two populations therefore remains only the statistically significant difference between the specific venom IgE levels of children with LLRs compared to those with SRs.

Venom specific IgE Abs represent a biological response that has at least partially protective aspects as, as now known, the mast cell reaction involves the release of mediators useful for the neutralization of hymenoptera venom and more [22-25]. Therefore, it is possible to consider that an excessive increase in IgE, also conditioned by predisposing, intercurrent and non-specific factors, can alter the fragile balance between protection and allergy. Since in our case series the difference was also highlighted considering the LLRs even compared to grade I and II honey bee venom induced SRs, it is possible to hypothesize that small increases in specific IgE are enough to produce an aggravation of the reaction but also little is enough to facilitate their decrease with subsequent clear



clinical improvement. This in fact happens very often in children. The direct correlation between specific IgE levels and the severity of the reaction is however not usual in the context of atopic diseases and what we have observed would indicate how this type of allergic reaction strictly depends on the immunogenic characteristics of the venom rather than on the personal predisposition of the individuals. In addition, this unexpected result could suggest the opportunity, if confirmed on a larger case study, to include the dosage of specific IgE in the monitoring of children with LLRs as one of the useful elements for determining the risk of a future more serious reaction.

### Statement of ethics

The study protocol was approved by the Ethics Committee of ASST Grande Ospedale Metropolitano Niguarda (Milan, Italy) on 26 October 2018, protocol ID 538-102018.

### Author contributions

All the authors have contributed equally in the design, data collection, realization and writing of this manuscript.

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