

Evaluation of the risk of anaphylactic reactions by wasp venom-extract challenges in children

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Diagnostic sting challenges have been shown to provide information on the risk of further anaphylactic reactions to bee stings. We present a follow-up study in wasp venom-hypersensitive children after diagnostic venom extract challenges to analyze their risk of further anaphylactic reactions. Responses were obtained from 104 patients with wasp venom hypersensitivity out of 115 former patients. Only one of the 104 patients showed more than a severe local reaction to the sting challenge irrespective of the performance of a single or sequential challenge; therefore, only one patient received venom immunotherapy. The performance of a diagnostic sting challenge with wasp venom extract in children had a high negative predictive value of 94.6% for the risk of further systemic reactions. This was shown by analysis of later field stings, since 37 children experienced further field stings and only two of these children (5.4%) developed a mild systemic reaction (urticaria) equal to or less severe than the index sting. The value of the venom extract challenge can be interpreted in two ways: either it is less sensitive than a native sting challenge since the rate of systemic reactions to the challenge was very low, or the prognosis of wasp venom hypersensitivity in children is extremely favorable. Since the latter hypothesis is supported by the low incidence of systemic field sting reactions, we postulate that venom immunotherapy is necessary only in a minority of children with wasp venom hypersensitivity with an index sting reaction of Mueller grade I or II. However, the value of venom extract challenges as a general diagnostic instrument in children with Mueller I and II reactions due to wasp venom hypersensitivity may be questioned. It may have a place as a safe procedure in demonstrating to parents and physicians the often self-limiting natural course in most of these children.

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The diagnostic procedures necessary to evaluate the risk of repeated anaphylactic reactions to insect stings with respect to the indication of venom immunotherapy (VIT) are controversial. Some authors conclude that VIT is necessary in only a minority of adult patients (1,2). This is especially true for children (3–5). Anaphylactic reactions to wasp venom (WV) are less frequent and have a smaller risk of recurrence than those to bee venom (BV) (6–11). Diagnostic sting challenges, although a rather invasive procedure, are the only parameter shown to provide information about the risk of further anaphylactic reactions to insect stings when compared to

medical history, total or specific IgE, specific IgG or intracutaneous skin test (3–6,9,10,12–17). While the diagnostic value of sequential native sting challenges for the indication of VIT could be demonstrated for children with bee venom hypersensitivity (5), there are no data on children with wasp venom hypersensitivity. The evaluation of native sting challenges versus venom extract challenges has not yet been performed in an intra-individual comparison study. Since such a study was judged unethical in children, we performed a follow-up study in WV-hypersensitive children without VIT after diagnostic venom extract challenges.

Table 1. Severity of reactions to accidental stings, and specific IgE and localization of index sting in wasp-hypersensitive children

Reactions	Definition of Mueller grades (18)	Index sting	WV-specific IgE (median; CAP)	Localization of index sting	
				Extremity/Trunk	Face/Neck
n		104		57	25
Local reaction	No systemic reaction	30 (28%)	3.0	16 (28%)	11 (44%)
Mueller I	Generalized urticaria	24 (23%)	3.0	12 (21%)	8 (32%)
Mueller II	Angioedema, vomiting	37 (36%)	3.0	26 (46%)	3 (12%)
Mueller III	Respiratory complications	10 (10%)	2.5	2 (4%)	2 (8%)
Mueller IV	Cardiovascular reactions	3 (3%)	3.0	1 (2%)	1 (4%)

Materials and methods

Patients

One hundred and fifteen patients who underwent a diagnostic sting challenge were included in the study. Every patient presenting with suspected insect venom hypersensitivity had been subjected to the following diagnostic algorithm (5). Index sting reactions were classified according to Mueller (Table 1) (18). Patients with reported reactions of Mueller grade III or IV received VIT without a sting challenge. In patients with Mueller grade I and II reactions and those patients with severe local reactions whose parents insisted on further diagnostic tests, in-hospital venom extract challenges were performed.

Baseline diagnostic evaluation

The initial evaluation consisted of the patient's medical history, a physical examination and total and venom-specific IgE measurement (CAP-System, Pharmacia, Freiburg, Germany). An intracutaneous skin test (ICST) with 0.1 ml of BV or WV extract (Reless[®]-wasp venom, Reless[®]-bee venom, ALK Scherax, Hamburg, Germany) at concentrations of 0.0001, 0.001, 0.01 and 0.1 µg/ml was performed intracutaneously on the patient's forearm before sting challenge. The test was discontinued if a positive result (weal ≥ 5 mm after 20 min) occurred.

Venom extract challenge procedures

Venom extract challenges were carried out with 100 µg of venom extract (Reless[®]-wasp venom, ALK Scherax, Hamburg, Germany) administered subcutaneously at the extensor side of the patient's upper arm. Since 1993, a second challenge has been performed after an interval of 4–6 weeks to detect possible booster reactions (sequential venom extract challenge). Systemic reactions to the challenge indicated the necessity for VIT. Patients with local reactions only did not receive VIT.

Study design

A questionnaire regarding reactions to subsequent field stings was sent to all patients who had received an in-hospital venom extract challenge between 1989 and 1997. The main questions included a complete history of all stings, including date, identification of the insect and severity of the reaction using a table of the characteristic symptoms, which could be marked for each sting. Parents were asked whether their children suffered from other clinically relevant allergies (atopic dermatitis, allergic rhinitis, bronchial asthma). Answers were either obtained by completion and return of the questionnaire or by a structured telephone interview using the same questionnaire.

Statistical analysis

Statistical analysis was performed with SPSS statistical software (SPSS for Windows 7.0, SPSS Inc., Chicago, Illinois, USA), using the Mann–Whitney *U* test and the χ^2 test for linear-by-linear association. A *p* value of less than 0.05 was considered to represent a significant difference.

Results

Patients

Answers were obtained from 90.4% of patients. The patients' mean age was 8.0 years (range 1.8–15.8). The male:female ratio was 2:1. A third of the children (35%) suffered from other allergies (allergic rhinoconjunctivitis, allergic bronchial asthma or atopic dermatitis). No statistical correlation with any of the evaluated parameters was observed. Mean total IgE was 148 kU/l (range 10–1157). Most patients had a WV-specific IgE of CAP class 2, 3 or 4 (31.6, 35.7 and 15.3%, respectively); 6.1% showed a WV-specific IgE of CAP class 5 or 6. One-third of the patients (31.2%) were also sensitized to BV (CAP ≥ 2). In 58.1% of the patients no BV-specific IgE (CAP = 0) could be demonstrated.

Index sting reactions

The severity of reactions of the children with WV hypersensitivity is reported in Table 1. No association could be demonstrated between the severity of the index sting (Mueller grade) and age, gender, WV-specific IgE, ICST or number of previous stings. The localization of the sting was the extremities in 70%, and the neck and face in 30%. The localization was not statistically significantly associated with the severity of the index sting (Table 1). For 41% of the patients, the index sting was reported to have been the first sting in the patient's life, while 37% of the patients had been stung several times before presentation to our department. The number of stings prior to the index sting did not influence the degree of sensitization significantly (Table 2). Taking only patients with systemic reactions to the index sting into account, specific IgE depended significantly on the number of previous stings ($p < 0.05$); with local reactions included the p value was 0.051. In 70%, patients or parents were convinced of having identified the insect as a wasp.

Venom extract challenge procedures

Most patients presented within the first year after the index sting (0–8 years, median 0.5). Forty-seven of the patients (45%) were subjected to a single challenge, were 57 (55%) subjected to a sequential venom extract challenge with WV. Only 12 patients (11% overall, five of whom were sequentially challenged) received an additional challenge with BV because data and history were ambiguous.

The threshold of a positive test result for the WV ICST ($n = 94$) was 0.001 $\mu\text{g/ml}$ for 10.6% of the patients. Almost half of the patients reacted to 0.01 $\mu\text{g/ml}$; 30.9% reacted only to 0.1 $\mu\text{g/ml}$ and 9.6% remained negative. The relationship of WV ICST results and WV-specific IgE was highly significant ($p < 0.001$), but neither value reflected the risk of anaphylaxis according to Mueller in

the index sting, venom extract challenge or later field sting (Table 1).

Only one girl showed more than a severe local reaction to the venom extract challenge irrespective of the performance of a single or sequential challenge (Table 3); therefore only this patient received VIT as a result of the challenge.

Field sting reactions

Thirty-seven children (35.6%) challenged with WV extract experienced further field stings, nine of them (24.3%) more than once. In 75%, the insect was identified as a wasp. Except for age, no statistically significant difference between re-stung patients and patients without experience of a further field sting was observed. However, the re-stung patients were significantly ($p < 0.001$) younger (median 6.7 years, range 2.1–15.4) compared to those who were not re-stung (9.2 years, range 1.8–15.4).

Thirty-five patients (94.6%) showed only local reactions following further field stings. Two of the children (5.4%) developed a mild systemic reaction, i.e. urticaria (Table 3), equally or less severe than the reaction to the index sting. The median time from challenge to field sting was almost 2 years and ranged from 2 months to more than 6 years.

Discussion

In children hypersensitive to WV, severe reactions to index stings are rare. Our results indicate that the risk of further systemic reactions in children with initial mild systemic reactions is low. Therefore, prognosis of WV hypersensitivity in children is favorable.

According to parents' reports, approximately one-third of the patients also suffered from other allergic diseases. This is in accordance with reports from other authors (4,6). The localization of the index sting was not associated with the severity of the index sting reaction. However, the percentage of patients with reactions classified as local reactions in the face or neck who were subjected to a venom extract challenge was higher than in patients with other local reactions in other localizations. Franken et al. retrospectively found a significantly higher number of patients with stings to neck or face having received a VIT than those without VIT (14). These findings might reflect the wish of parents and physicians to evaluate and prevent the further risk of systemic reactions due to the sometimes threatening appearance of these reactions.

Table 2. Sensitization and number of stings prior to index sting in wasp-hypersensitive children (number of patients)

	Number of stings prior to index sting		
	0	1	> 1
n	37	20	34
CAP 0	5	0	1
CAP 1	3	1	0
CAP 2	11	6	11
CAP 3	11	6	16
CAP 4	6	6	3
CAP 5	1	1	1
CAP 6	0	0	2

Table 3. Severity of accidental stings and venom-extract challenges in wasp-hypersensitive children

Reactions	Index sting	1st Challenge	2nd Challenge	Field sting
n	104	104	57	37
Local reaction	28%	99%	100%	94%
Mueller I	23%	1%	0%	6%
Mueller II	36%	0%	0%	0%
Mueller III	10%	0%	0%	0%
Mueller IV	3%	0%	0%	0%

Neither history nor total or specific IgE or ICST results predicted the severity of a further insect sting reaction. This has been shown before by other authors (3,5,10,12,19). Three (2.9%) of our WV-hypersensitive patients had no WV-specific IgE but positive ICST. Six patients (5.3%) had a negative ICST but were sensitized to WV. Such differing results have also been observed by others (20,21). Patrizzi et al. (21) found that 24.3% of 33 BV hypersensitive patients had a positive ICST but no specific IgE. Only one patient had a negative skin test but specific IgE. In the literature, patients with documented anaphylaxis to insect stings but without signs of hypersensitivity in ICST or IgE account for up to 10% of patients (9). This demonstrates the need for more reliable diagnostic tools.

Venom extract challenge procedures

Sting challenges are frequently performed with living insects, which has two major advantages. Firstly, the venom contains a variety of other substances, such as histamine, which might influence the clinical reaction. However, the aim of a venom extract challenge is to evaluate the indication for VIT, which is administered to induce tolerance to the allergen. This is not induced by the toxic components of the venom. Thus, the result of the venom extract challenge may give a more reliable answer than a native sting challenge. Secondly, the psychological effect of a negative sting challenge is more convincing. However, there are also several disadvantages of native sting challenges, especially concerning wasps. These include the varying amount of venom delivered. Sting challenges with wasp are also complicated by their seasonal availability and the difficulty of catching the insects (12,16,22).

Only one girl in the study showed more than a severe local reaction to the venom extract challenge irrespective of single or sequential challenge and developed urticaria several hours after the first venom extract challenge. VIT was started without an additional challenge. No anamnestic or diagnostic parameter indicated the more severe reaction. We conclude that the low incidence of

reactions to the venom extract challenge is not due to inadequacy of the instrument.

For venom extract challenges in children with BV hypersensitivity, Hauk et al. (5) found a higher frequency of reactions (11.2% mild, 1.6% severe) to the first of a sequential sting challenge, and 8.0% and 8.8% respectively in response to a second challenge in BV hypersensitive children. WV challenges in WV-hypersensitive children in the study by Hauk et al. induced no systemic reactions in the first challenge and 6% in the second challenge.

We interpret differing results from a comparison of our data in children to those of adult patients with WV hypersensitivity (17) as due to better prognosis of hypersensitivity to WV than BV and of the disease in children than in adults rather than due to the sensitivity of our venom extract challenge.

Field sting reactions

Thirty-seven patients (35.6%) challenged with WV extract experienced a subsequent field sting. Re-stung patients were significantly younger, which we interpret as due to the higher attention older children pay to their environment. Two of the re-stung children developed a mild systemic reaction (urticaria). One of the two children was a 7.1-year-old boy with a specific WV of CAP class 4 and a positive reaction to WV-ICST at 0.01 µg/ml WV. At his first insect sting, he had been stung by three wasps at once and experienced a generalized urticaria after 5–15 min. After the venom extract challenge he was re-stung on three occasions. Two stings induced only local reactions. However, he was once again stung by three wasps at once and again experienced a generalized urticaria. The other patient was a 7.9-year-old boy with a Mueller II reaction to his index sting. He had a specific WV CAP class 4 and a positive WV-ICST response to 0.01 µg/ml WV. After 1.4 years he was re-stung under his left eye and developed a generalized urticaria and a large local reaction. He presented again to our department and VIT was started. No parameter had indicated the risk for further systemic reactions.

The negative predictive value of our venom extract challenge procedure is therefore 94.6%. Blaauw et al. (17) found a value of 89.8% in adults with WV hypersensitivity of Mueller I to IV reactions, van Halteren et al. found a value of 95% in adults with hymenoptera hypersensitivity (16), and Hauk et al. found a negative predictive value of 97.4% (5) in children with BV hypersensitivity. The major difference of our findings is that the indication for VIT in our study with WV-hypersensitive children is extremely strict, 1/104 versus 9% (5) and 27% (17), respectively. Thus, the value of the venom extract challenge can be interpreted in two ways: either its sensitivity is lower than that of a native venom extract challenge for the reasons discussed above, or the prognosis of WV hypersensitivity in children is extremely favorable. The latter hypothesis is supported by the low incidence of 5.4% Mueller I field sting reactions in WV-hypersensitive children without VIT.

In conclusion, our results indicate that the risk of repeated systemic reactions in WV-hypersensitive children is low, as shown by venom extract challenge with a negative predictive value of 94.6%. Therefore, VIT is only necessary in a minority of children. Due to the favorable prognosis, the value of the venom-extract challenge as a general diagnostic instrument in young patients with WV hypersensitivity Mueller I and II reactions may be questioned. It may have a place as a safe procedure in demonstrating to parents and physicians the often self-limiting natural course in most WV-hypersensitive children.

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