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Hymenoptera stings in the head region induce impressive, but not severe sting reactions

Short title: *Risk factors for severe systemic sting reactions*

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ABSTRACT

Stings in the head region are considered to be a risk factor for severe systemic reactions to Hymenoptera stings. We supposed that stings in skin areas, which are well supplied with blood, lead to more severe reactions and tested our hypothesis in 847 patients with confirmed Hymenoptera venom allergy.

However, symptom severity was independent from sting site: only 16.3% of patients with severe reactions were stung on the head ($p=0.017$). But we confirmed age > 40 years ($p<0.001$) as well as elevated basal tryptase levels ($p=0.001$) as risk factors.

Taking antihypertensive drugs seemed to have an influence: 41.7% of patients taking antihypertensive drugs experienced a severe reaction compared to 29.5% of patients, not taking such drugs ($p=0.019$). However, considering patients' age in regression analysis, taking antihypertensive drugs had no effect on symptom severity ($p=0.342$). Importantly, in most patients with severe reactions, cutaneous signs were absent ($p<0.001$).

KEYWORDS

age; antihypertensive drugs; head; severe systemic sting reaction; sting localization;

The rate of reported systemic sting reactions (SSR) is 3.3% in Austria (1) and ranges from 0.3 to 7.5% in European epidemiological studies. (2) Various risk factors have been described like higher age, elevated basal tryptase levels, insect type, cardiovascular disease, drugs like β -blockers or sting site. (2-6) Stings on the head, neck or throat were discussed to account for most fatal reactions and stings in these parts are believed to result in more severe SSR than stings on the extremities. (6, 7) However, there is no recent data available for a large, central European study cohort including children and adults. Therefore our aim was to evaluate, if there is a relation between sting localization and symptom severity and we hypothesized that

stings in skin areas, which are well supplied with blood, lead to more severe reactions. Furthermore we aimed to determine risk factors for severe SSRs and verify the previously published risk factors in our study cohort.

A total of 847 patients (50.1% men, 49.9% women) with confirmed hymenoptera venom allergy were included in the study. The patients ranged in age from 9 to 85 years, with a mean age of 45 years (see Online Supplement 1: demographic data table). Patients were asked about sting localization and symptoms using a standardized questionnaire (see Online Supplement 2). Systemic sting reactions were classified according to Ring and Messmer (8), grade III and IV reactions were considered to be severe reactions. In order to determine the stinger's depth of penetration, we used excess skin after excision of skin tumors in two patients and performed sting challenges with bees.

Sting reactions were predominantly mild or moderate: 55 (6.5%) had grade I, 522 (61.6%) grade II, 257 (30.3%) grade III and 6 (0.7%) grade IV reactions. While the mean time span between the sting and the appearance of mild systemic reactions was 15 min (lower and upper quartiles: 10.00; 30.00), severe systemic reactions occurred already after 6.5 min (3.00;10.00; $p<0.001$). As expected, the number of stings had no effect on the severity of the reaction ($p=0.843$). Among the 263 patients who experienced severe SSRs, the distribution concerning sex was balanced (138 (52.5%) men and 125 (47.5%) women). Interestingly, men were more likely stung on the head than women: 93 (62.0%) men and 57 (38.0%) women ($p<0.001$) reported a sting on the head. However, we could definitely not confirm previous reports of higher risk for severe SSRs after stings on the head or neck: 16.3% of patients with severe SSRs were stung on the head, compared to 83.7% (14.9% on trunk, 39.1% on upper extremities, 29.8% on lower extremities) stung on other parts of the body (odds ratio [OR]: 1.69; 95% confidence interval [CI]: 1.11-2.57; $p=0.096$). The relative frequency of severe SSR (head versus other sting sites) was 23.5% and 34.2%, respectively ($p=0.017$). As shown

in Figure 1, the stinger's depth of penetration depends on the part of the body. The stinger in the back got stuck in the rarely supplied reticular dermis, whereas the stinger in the face reaches the deep arteriovenous plexus of the subcutis. We therefore expected more frequent severe reactions to stings in well supplied areas with thin reticular dermis. However, symptom severity was independent from skin thickness.

Different observations were made concerning type of venom and severity of reactions: while one group reported a higher risk for vespid venom allergic persons (4), the other states that the risk for severe reactions is higher in patients sensitized to honeybee venom. (2) In our study, 27.4% of patients with bee venom allergy developed a severe SSR compared to 32.2% of wasp venom allergic persons ($p=0.335$), indicating that type of venom cannot be correlated with symptom severity. Furthermore, neither a higher number of bee stings nor wasp stings has an influence on the severity of the reaction ($p=0.509$ and $p=1.000$, respectively).

In general, severe SSRs are less frequently observed in children compared to adults and higher age, from about 40 years onwards, is considered to be a risk factor. (2-6) This is even true for our study cohort: 189 (71.9%) patients older than 40 years reported a severe SSR compared to 74 (28.1%) younger patients (OR: 2.01; CI: 1.47-2.75; $p<0.001$).

96 patients were taking antihypertensive drugs (ACE inhibitors and/or β -blocker) when they were stung. While 41.7% of these patients experienced a severe SSR, this only happened to 29.5% of patients who were not taking antihypertensive drugs ($p=0.019$). Importantly, this result is biased by patients' age: only 4.2% (4/96) were younger than 40 years. Considering patients' age in regression analysis, taking antihypertensive drugs had no effect on symptom severity ($p=0.342$). Anyway this effect has to be verified in a larger study cohort.

As mentioned previously, another risk factor for severe SSRs is an elevated basal tryptase level (BTL). (2-5) An elevated BTL exceeding 11.4 ng/ml was found in 55/831 (6.6%) patients and was significantly correlated with severity of the reaction: only 29.5% of patients

with normal BTL had a severe SSR compared to 52.7% of patients with elevated BTL (OR: 2.66; CI: 1.54-4.62; $p=0.001$). Importantly, this result is not influenced by patients' age. If we consider patients' age in regression analysis, elevated BTL still correlate with severe SSR ($p=0.002$). In our study cohort, a highly significant correlation between the severity of the reaction and the absence of urticaria or angioedema could be demonstrated: in about 75% of patients with severe SSRs, cutaneous signs were absent (see Table 1). Interestingly, elevated BTL can be correlated with the presence of urticaria: 80.0% of patients with elevated BTL had no urticaria compared to 54.3% with normal BTL ($p<0.001$). These findings were also made by Stoevesandt et al. (5) However, there was no statistically significant correlation between BTLs and angioedema ($p=0.071$).

From our data and previously published results, it can be assumed that only a few factors really have an influence on the severity of sting reactions (see Online Supplement 3: Classification and Regression tree). We could not confirm that stings on the head or neck more frequently result in severe SSRs. This was also reported by an Australian study. (9) Sex and type of venom had no influence as well. Taking antihypertensive drugs is no risk factor for severe SSRs and this was also reported by another study. (5) However, we were able to show that this effect is caused by patients' age since taking such drugs is associated with older age.

But there are at least two factors which can be used as predictors for severe SSR: people older than 40 years and people with elevated basal tryptase level have a higher risk for severe systemic reactions to Hymenoptera stings. Importantly, in most of the patients with severe SSRs urticaria or angioedema was absent. If our findings are also true for children, needs to be clarified in another study with a larger study cohort, including more children.

Author contributions

LA and GS participated in all stages of the study and were the main authors of the manuscript. DB, IS, CS acquired the data. MH provided skin biopsies and CM histological pictures. WA revised the manuscript. All authors contributed with interpretation of the data, revised the article critically, and gave final approval.

TABLE

Table 1: Correlation of symptom severity and skin symptoms

	Urticaria		Angioedema	
	No	Yes	No	Yes
Grade I & II	277 (48.0%)	300 (52.0%)	374 (64.8%)	203 (35.2%)
Grade III & IV	193 (73.4%)	70 (26.6%)	203 (77.2%)	60 (22.8%)
	$p<0.001$		$p<0.001$	
	OR: 0.34; CI: 0.24-0.46		OR: 0.55; CI: 0.39-0.76	

FIGURE LEGEND

Figure 1: The stinger in the back got stuck in the reticular dermis, whereas in areas with thin reticular dermis like the face, the stinger reached the deep arteriovenous plexus of the subcutis.

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