

Shortness of interval between two stings as risk factor for developing Hymenoptera venom allergy

Pucci S, Antonicelli L, Bilò MB, Garritani MS, Bonifazi F. Shortness of interval between two stings as risk factor for developing Hymenoptera venom allergy.

Allergy 1994; 49: 894–896. © Munksgaard 1994.

The aim of the study was to determine whether a short interval (<2 months) between two consecutive stings influences the development of Hymenoptera venom allergy. The study compared the sting-interval distribution in 120 allergic patients who experienced a first-time systemic reaction to a Hymenoptera sting, and in 100 healthy controls. A significant difference in sting-interval distribution between the two groups was found ($P = 0.0001$). In 71 of 120 allergic patients, the sting that provoked the systemic reaction had been preceded by another, completely tolerated sting not more than 2 months before. However, in the control group only four subjects out of 100 had received two consecutive stings within less than 2 months. In conclusion, a short interval between two consecutive stings seems to be a risk factor for the onset of Hymenoptera venom allergy.

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Key words: insect allergy; natural history; risk factor; time interval.

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Accepted for publication 28 April 1994

Epidemiologic studies in both the USA and Europe have revealed that the prevalence of Hymenoptera venom allergy in the general population ranges between 0.8 and 4% (1, 5, 6, 19). The natural history of the disease has been extensively investigated in retrospective and prospective studies (reviewed in Ref. 17). On the other hand, few data are available on the genetic and environmental factors that may be involved in the production and persistence of IgE antibodies in subjects stung by Hymenoptera.

As regards genetic factors, the familial aspects in the development of the disease have been described (9); a possible protective role of black race has also been suggested (13). In addition, protection linked to human lymphocyte antigen (HLA)-DR4 and DQw3 alleles, whose presence is associated with the inability to synthesize IgE against two important venom allergens (phospholipase A₂ and melittin), has been shown (12).

As for environmental factors, the total number of stings appears to play a central role in Hymenoptera venom sensitization. This observation is consistent with both the fact that most Hymenoptera-allergic patients live in rural areas and the high prevalence of sensitization in beekeepers (1, 2, 11, 14, 16, 23). However, the risk of sensitization in beekeepers is

inversely proportional to the total number of stings received per year. It has been shown that beekeepers stung more than 50 times in a season do not develop any allergic reaction because they undergo "spontaneous desensitization" (3).

Current opinion supports the hypothesis that a temporal factor of antigen administration influences the development of anaphylactic reactions (22). Since Hymenoptera venom allergy allows identification of the interaction times between antigen and the immune system, we wanted to determine whether the time interval between two consecutive stings can affect the development of venom allergy.

Material and methods

A retrospective study was done on 120 patients (98 men and 22 women) with a mean age of 38 years (range: 9–75 years) allergic to Hymenoptera venom (73 vespids and 47 honeybees). The patients were selected according to the following criteria:

- first systemic allergic reaction to a Hymenoptera sting (reactions were graded according to Mueller's classification (15))
- previous sting (or stings) perfectly tolerated
- positive identification of the stinging insect (pa-

tients whose threshold skin reactivity or RAST were equal for *Apis mellifera* and *Vespula* species venoms were excluded from the study).

The diagnosis was made by intradermal testing, with increasing venom dilutions ranging from 0.001 to 1.0 µg/ml. The following Hymenoptera venoms were used; *A. mellifera*, *Vespula* species, and *Polistes* species (Pharmalgen ALK, Denmark); specific serum IgE against these venoms was also determined (Phadebas RAST, Pharmacia, Uppsala, Sweden).

The patients were divided into two groups according to the time interval (<2 months or >2 months) between the sting that provoked the allergic reaction and the antecedent sting that was completely tolerated.

One hundred healthy subjects were used as a control, mostly family members of the patients (47 men, 53 women), with a mean age of 42 years (range: 10–81 years), who had been stung on repeated occasions without any allergic reactions. The control group was mostly composed of farmers or their family members, who could identify with certitude the stinging insect. In such subjects, the distribution of time interval between consecutive stings (<2 months or >2 months) was also studied.

Statistical analyses

The statistical tests used were the chi-square test and the *t*-test for unpaired data. Differences were considered to be significant for $P < 0.05$.

Results

In 71 out of 120 allergic patients, the sting that provoked the systemic reaction had been preceded by another, perfectly tolerated sting not more than 2 months before. On the other hand, in the control

group, only four subjects out of 100 had received two consecutive stings in less than 2 months. A significant difference in distribution of sting intervals between the two groups was found ($P = 0.0001$).

A further subdivision of the allergic patients, based on various time intervals between two stings (0–2, 2–12, 12–24, or >24 months), confirmed that the highest risk was related to the shortest time interval. Moreover, a homogeneous patient distribution in the intervals greater than 2 months was shown (Fig. 1). In the allergic group, the mean age of 71 short-sting-interval patients (34 ± 12 years) was significantly lower than the mean age (43 ± 14 years) of the remaining 49 patients having a longer sting interval ($P < 0.001$). No significant differences in sex, atopy, kind of stinging insect, reaction severity, skin reactivity, or RAST class were found.

Discussion

Retrospective studies suggest that, after the initial sting reaction, the time interval of successive re-stings does not influence the natural history of the disease (13, 18). However, the selection criteria in such studies may have been erroneous, because the nonreacting patients exposed to a subsequent sting did not return for reexamination. Additionally, it has been reported that a re-sting occurring within 3–4 weeks after an allergic reaction to a Hymenoptera sting may be asymptomatic, thus suggesting the existence of a “refractory phase” (20).

Our data suggest that a short time interval (<2 months) between the innocuous sting and the successive sting that leads to a systemic reaction appears to be a risk factor in the development of Hymenoptera venom allergy. Our findings are consistent with the high risk of sensitization in those categories subject to a high degree of exposure, such as beekeepers. Many studies have reported that the prevalence of allergic reactions to stings in beekeepers was considerably higher than those observed in the general population (2, 11, 14, 16, 23). Short sting intervals are evidently much more common among beekeepers than among the general population, and this fact may offer indirect confirmation of our findings.

Furthermore, in our study, the mean age of the 71 allergic patients included in the short-time-sting-interval group was significantly lower than that of the remaining 49 patients. This could be related to a difference in immunologic reactivity or, more probably, to the fact that younger people are at greater risk of exposure to stings (1, 7, 13, 17).

The sensitization risk to bee venom in nonallergic subjects has been evaluated in one prospective study (10). This study involved 29 nonallergic, healthy volunteers who received a total dose of 250 µg of pu-

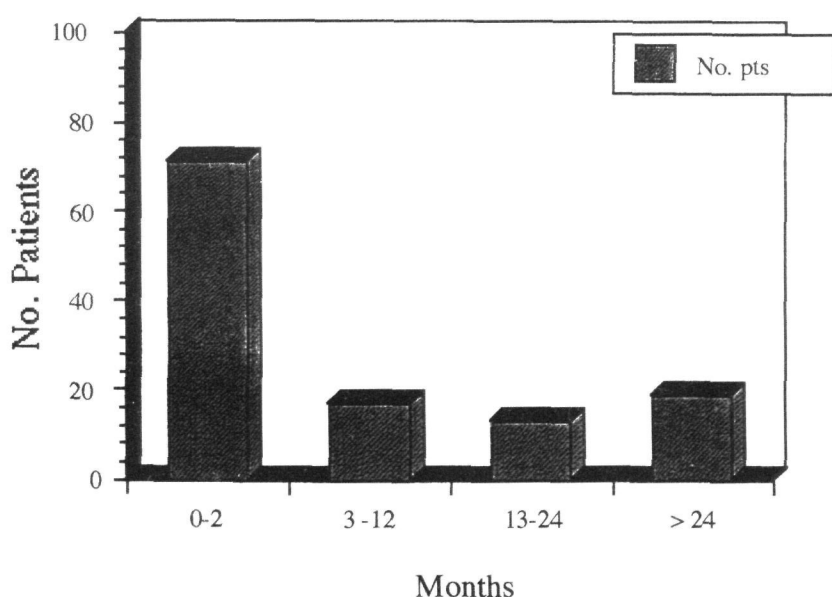


Fig. 1. Distribution of patients in reference to time interval between two successive Hymenoptera stings.

rified bee venom. Specific IgE production was noted in 13.7% of the subjects after one injection and in 31% after two injections; IgE levels tended to decrease after a few months in all subjects. Such findings were compared with the prevalence of clinical venom reaction (6.8%) in the general-population control. The authors hypothesized that the difference in percentage between the sensitization (31%) and the development of clinical reactions (6.8%) could be explained by the fact that not all the venom-sensitized patients were re-stung by a bee during the period in which specific IgE was present.

The hypothesis of transient sensitivity was also suggested in some epidemiologic studies to explain the difference between the high sensitization rate to venom and the relatively low prevalence of the disease (7, 8, 21).

Consistent with the above data, we believe that, in some patients, a short re-sting interval increases the likelihood of finding IgE levels prone to clinical reaction. Furthermore, in our study, after the first 2 months, patient distribution was homogeneous, and no relationship between the re-sting interval and the development of venom allergy was found (Fig. 1). Such data suggest that a difference may exist in the immune response pattern to venom allergens between the two groups. Although some aspects of venom-specific IgE synthesis have been studied (4, 12), the factors that regulate the persistence of such antibodies after a sting in man remain unknown.

In conclusion, in some subjects, the time interval between two consecutive stings can affect the onset of Hymenoptera venom allergy; further studies will be necessary to assess the degree of risk and the clinical outcome in such patients.

Acknowledgment

The authors thank Mrs Simonetta D'Andrea for technical collaboration.

References

1. ANTONICELLI L, PUCCI S, PIERETTI C, et al. Epidemiologia della patologia da puntura di imenotteri nella Regione Marche. *Folia Allergol Immunol Clin* 1989; 36: 43-51.
2. BOUSQUET J, COULOMB Y, ROBINET-LEVY M, MICHEL FB. Clinical and immunological surveys in beekeepers. *Clin Allergy* 1982; 12: 331.
3. BOUSQUET J, MENARDO JL, AZNAR R, ROBINET-LÉVY M, MICHEL FB. Clinical and immunological survey in beekeepers in relation to their sensitization. *J Allergy Clin Immunol* 1984; 73: 332-40.
4. CARBALLIDO JM, CARBALLIDO-PERRIG N, TERRES G, HEUSSER CH, BLASER K. Bee venom phospholipase A₂-specific T cell clones from human allergic and non-allergic individuals: cytokine patterns change in response to the antigen concentration. *Eur J Immunol* 1992; 22: 1357-63.
5. CHARPIN D, VERVLOET D, HADDI E, et al. Prevalence of allergy to Hymenoptera stings. *Allergy Proc* 1990; 11: 29-32.
6. GOLDEN DBK, VALENTINE MD, KAGEY-SOBOTKA A, LICHTENSTEIN LM. Prevalence of Hymenoptera venom allergy. *J Allergy Clin Immunol* 1982; 69: 124.
7. GOLDEN DBK, MARSH DG, KAGEY-SOBOTKA A, et al. Epidemiology of insect venom sensitivity. *JAMA* 1989; 262: 240-4.
8. GOLDEN DBK, ADDISON BI, KWITEROVICH RN, et al. Natural history of Hymenoptera venom allergy (HVA) in adults [abstract]. *J Allergy Clin Immunol* 1992; 89: 291.
9. HECHT F. Familial hypersensitivity to insect sting. *Lancet* 1971; ii: 496.
10. JARISH R, ZAJC J, BUZATH A. The risk of sensitization of non-allergic persons to bee-venom. *Arch Dermatol Res* 1982; 273: 173-4.
11. LIGHT WC, REISMAN RE, WYPYCH JI, ARBESMAN CE. Clinical and immunological studies in beekeepers. *Clin Allergy* 1975; 5: 383-95.
12. LYMPANY P, KEMENY M, WELSH KI, TAK HL. An HLA-associated nonresponsiveness to melittin, a component of bee venom. *J Allergy Clin Immunol* 1990; 86: 160-70.
13. LOCKEY RF, TURKELTAUB PC, BAIRD-WARREN IA, et al. The Hymenoptera venom study. I. 1979-1982: demographics and history-sting data. *J Allergy Clin Immunol* 1988; 82: 370-81.
14. MIYACHI S, LESSOF MH, KEMENY M, GREEN LA. Comparison of the atopy background between allergic and non-allergic beekeepers. *Int Arch Allergy Appl Immunol* 1979; 58: 160-6.
15. MUELLER HL. Diagnosis and treatment of insect sensitivity. *J Asthma Res* 1966; 3: 331-3.
16. MÜLLER U, SPIESS J, ROTH A. Serological investigations in Hymenoptera sting allergy: IgE and hemagglutinin antibodies against bee venom in patients with bee sting allergy, beekeepers and non-allergic blood donors. *Clin Allergy* 1977; 7: 57-64.
17. MÜLLER U. Clinical presentation and pathogenesis. In: MÜLLER U, ed. *Insect sting allergy*. Stuttgart: Gustav Fischer Verlag, 1990: 58-65.
18. REISMAN RE. Natural history of insect sting allergy: relationship of severity of symptoms of initial sting anaphylaxis to re-sting reactions. *J Allergy Clin Immunol* 1992; 90: 335-9.
19. SETTIPANE GA, BOYD GK. Prevalence of bee sting allergy in 4994 boy scouts. *Acta Allergol* 1970; 25: 286-91.
20. SETTIPANE GA, CHAFEE FH. Natural history of allergy to Hymenoptera. *Clin Allergy* 1979; 9: 385-90.
21. STUCKEY M, COBAIN T, SEARS M, CHENEY J, DAWKINS RL. Bee venom hypersensitivity in Busselton. *Lancet* 1982; ii: 41.
22. WASSERMAN SI, MARQUARDT DL. Anaphylaxis. In: MIDDLETON E, REED C, ELLIS EF, ADKINSON NF Jr, YUNGINGER JW, eds. *Allergy: principles and practice*. St Louis, MO: Mosby, 1988: 1365-76.
23. YUNGINGER JW, JONES RT, LEIFERMAN KM, PAULL BR, WELSH PW, GLEICH GJ. Immunological and biochemical studies in beekeepers and their family members. *J Allergy Clin Immunol* 1978; 61: 93-101.

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