

Venom-specific IgG antibodies in bee and wasp allergy: lack of correlation with protection from stings

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Summary

This paper investigates the relationship between venom IgG levels and protection from stings. Venom-specific IgG antibody levels have been measured by radioimmunoassay in untreated wasp- ($n=38$) and bee-allergic ($n=16$) patients presenting with systemic reactions to stings and in a sub-group of these (wasp = 15; bee = 9), before and after the initial course of venom immunotherapy (VIT). A history was taken of all reactions, the last systemic reaction being graded on a scale of 1-8 and of the number and timing of stings. In untreated patients venom IgG levels were much higher in bee-allergic patients (mean $\pm$ s.e. = $68.2 \pm 7.1\%$ positive pool) than in the wasp group ($27.1 \pm 4.2\%$) ($P < 0.05$ Mann-Whitney U-test). There was a marked rise in venom IgG after the initial course of VIT in the wasp group (geometric mean and 95% confidence intervals = 40.5%, 28.8-54.3) but a much smaller rise in the bee group (15.3%, 6.6-24.1), with no overlap in the 95% confidence intervals. Bee patients, who were mainly beekeepers or their relatives, had been more heavily immunized with venom than wasp patients. They had received: (i) more stings (mean number of stings: bee, 26; wasp, 4; $P < 0.001$) and (ii) more stings per year. Wasp patients received their smaller number of stings over a much longer period, up to 40 yr. There was no correlation between the severity of the last systemic reaction and the venom IgG levels alone or venom IgG and IgE levels in combined analysis in either bee or wasp patients. This study shows that the pattern of IgG response differs in bee and wasp-allergic subjects, and that most bee-allergic subjects with systemic reactions have high levels of venom IgG. The degree of immunization with venom seems to be an important determinant of the venom IgG level. Our findings suggest that venom-specific IgG levels do not predict systemic reactions to stings and are not useful for monitoring VIT. If protection from stings is IgG-mediated, our observations suggest that the relevant immune response is more complex, possibly involving IgG sub-classes, IgG antibodies to individual venom antigens or antibody affinity, and not adequately reflected by measurement of the concentration of venom-specific IgG.

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Introduction

The mechanism of immunotherapy is unclear; however, for many years it has been suggested that immunotherapy works by inducing specific IgG (blocking) antibody. Although controversial, this view is most widely accepted in the case of insect venom immunotherapy. Several lines of evidence have led to this belief. The early controlled trials with pure venom showed a high level of efficacy

(about 95% success in the venom-treated group and about 40% improvement after placebo) [1,2]. A number of studies showed that there was a marked rise in the level of venom-specific IgG in patients treated with venom extracts [3-5].

In a search for correlates of successful venom immunotherapy Golden *et al.* [6], using a lower dose regime which resulted in more failures, found that only the level of venom-specific IgG discriminated between successful and unsuccessful treatment. They found a higher level of yellow jacket-specific IgG in successfully treated patients

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affinity and titre of IgG4 to PLA2 after bee VIT, whereas the affinity of IgG1 and possibly also IgE antibodies decreased. In addition to IgG antibody, other factors which may contribute to the response to stings include end-organ sensitivity and the concentration, affinity and specificity of specific IgE.

The comparison between our RIA and the Pharmacia RAST assay for venom IgG showed a reasonable correlation. This was better for wasp than bee. This was included so that our findings could be compared with other published studies in which the IgG RAST assay is used. The latter test is thought to detect too much low affinity antibody binding.

We recognize that a disadvantage of this study is that the venom antibody levels were not measured at the time of the systemic reaction, and that it can be argued that some of the IgG may have been generated as a result of the last sting. However, it was the bee-allergic group who had the highest IgG levels (untreated), and they had been stung many times (a mean of 26 stings per person) so that it is unlikely that the last sting changed the IgG level significantly. In addition, if one considers the interval between the last sting and the test date, this was similar in both the bee group (with high venom IgG) and the wasp group (with low venom IgG levels), especially in the sub-group of patients who had received their stings in the preceding 2 yr. Furthermore, our findings are in agreement with others where the venom-specific IgG was measured at the time of sting challenge. Another criticism might be that we did not carry out a sting challenge to demonstrate that patients were still sensitive. It is of interest that when sting challenges have been carried out on more than one occasion in some subjects [13] the result may be variable, with no reaction or a systemic reaction. This inconsistency of response raises problems when relating sting challenge to venom IgG levels.

An observation of considerable surprise was that occasional patients, in whom the interval between the last sting and the test date exceeded 2 yr, had high venom-specific IgG levels (e.g. JL 87%, JA 94%).

Our observation of a different IgG response in bee and wasp venom-allergic patients, with a low level in untreated wasp patients rising with immunotherapy and a high pre-treatment level in bee-allergic patients little changed by immunotherapy, is in agreement with Kemeny *et al.* [24]. This may, in part, explain discrepancies between studies, if data from bee- and wasp-allergic subjects were not analysed separately. Of the studies showing no correlation between venom IgG levels and protection, two involved only bee patients [12,20] and two involved both bee and wasp [10,11] while those demonstrating a correlation involved mainly yellow jacket-allergic subjects [6,13]. Our data, however, suggest that

measurement of the venom-specific IgG concentration is of no value in predicting protection from stings in either bee- or wasp-allergic patients and is not helpful for monitoring VIT. A determinant of the venom IgG level in untreated patients is the degree of immunization to venom.

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