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IgE Antibodies to Tetanus Toxoid in Relation to Atopy

Key Words

Vaccination
Atopy
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IgG4
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Abstract

In approximately 25% of subjects receiving tetanus booster immunization (4 study groups A–D with $n = 6, 25, 50$ and 240 , respectively; age 18–40 years for groups A–C, age 2 for group D), substantial IgE antibody levels were found. In groups A and B, sequential serum samples were available for analysis. The IgE response peaked before the IgG response and was often higher at week 1 than at week 2. The 6 subjects in group A (military recruits) received 2 booster injections. At the time of the second injection, 2 subjects had a very high IgE antibody titre (as well as a high IgG antibody titre), but no signs of an allergic reaction were noted. A significant association with atopy-related factors was found, but many apparently non-atopic subjects developed IgE antibodies.

Introduction

The high incidence of an immediate-type skin reactivity [1–3] or IgE antibodies [4–6] following booster vaccination with tetanus toxoid (TetTox) and diphtheria toxoid (DipTox) has not been widely appreciated. This neglect is undoubtedly due in part to the low incidence of allergic reaction following these vaccinations. Furthermore, the assay itself presents some difficulties, because of the relatively high concentration of antibodies of other isotypes, predominantly IgG1, which interfere in the IgE antibody assay, unless either a large amount of toxoid is used per test, or the sample is pretreated to remove interfering IgG.

We feel (as did Fireman and coworkers [3, 5]) that toxoid vaccination is a useful model to study the human IgE response in vivo and to pinpoint the similarities and differences between atopics and non-atopics.

Materials and Methods

Subjects

Group A ($n = 6$) consisted of military recruits who received a routine injection course with DT on AlPO₄. Blood samples were obtained on days 0, 14 and 26; a second injection was given on day 26 and further blood samples were obtained on days 34, 41 and 63.

Group B ($n = 25$) consisted of laboratory personnel, aged 18–40 years. These subjects were boosted with 5 Lf TetTox adsorbed on AlPO₄. Blood samples were obtained on days 0, 3, 7, 14 and 84.

Group C ($n = 50$) consisted of residents of the Van der Bergh-Stichting. These blood samples were obtained in the course of an investigation into the effects of diphantoin on immune responsiveness. Twenty-five of the subjects did not receive the drug, but served as controls. Since no effect of the drug treatment on the immune response was observed, all subjects were considered to belong to one single group. The booster vaccination was performed with DT on AlPO₄. Serum samples were obtained on days 0 and 14.

Group D ($n = 240$) was part of a cohort of children in Germany followed from birth; details of this cohort will be presented elsewhere. For the present study, it is relevant to note that the vaccination history of these children was variable. At the time of blood sampling (age 24 months) all included infants had received 2, 3 or 4DT vaccinations (alum absorbed). Subjects who had *Bordetella pertussis* included in one or more of the vaccinations were excluded from the present analy-

sis, as were subjects who received the last vaccination less than 6 days or more than 300 days before blood sampling.

Antibody Assays

IgE antibodies were measured by a radioallergosorbent test (RAST), performed essentially as described elsewhere [7]. The antigen was coupled to CNBr-activated Sepharose (Pharmacia; 1 mg protein/g Sepharose; 1 mg corresponds to 1,500 Lf TetTox and 1,800 Lf DipTox; the fluid toxoids were kindly provided by the Rijksinstituut voor Volksgezondheid en Milieu, Bilthoven, The Netherlands). The Sepharose was suspended at 2 mg/ml in PBS containing 10 mM EDTA, 0.2% Tween 20 and 0.05 mg/ml NaN₃. The results were read from a standard curve calibrated in IgE IU/ml by comparison with a chimeric mouse/human IgE antibody to Der p 2 [see Schuurman et al., this volume]. For each subject, the highest results of either of the two toxoid RASTs was used for analysis.

Results and Discussion

When we used 1 IU specific IgE as a cut-off point (corresponding to approximately 5% binding of the labelled anti-IgE, well above the background of 2% label binding), we found an IgE antibody response to DipTox and/or TetTox in 4/6 of group A, 13/25 of group B, 22/50 of group C and in 122/240 of group D. This high response rate of 50% already indicates that the production of IgE antibodies to these toxoids is not restricted to subjects with an atopic background. This was confirmed by comparing the responses in subjects with or without IgE antibodies to common inhalants (and for the infants in group D for foods as well). As is shown in group D in figure 1, a quantitative difference in the IgE response was found, but very high IgE antibody scores (occasionally >30 IU toxoid-specific IgE) were also found in otherwise RAST-negative subjects. Subjects with an elevated total IgE were more often found to produce IgE to the toxoids, but some subjects with a total IgE level <10 IU/ml were found to produce antitoxoid IgE (fig. 1). Very similar results were found in the other three groups.

As expected, a significant correlation (Spearman $\rho = 0.76$, $n = 161$) was found between IgE responses to TetTox and to DipTox. Less easy to explain was the finding that some subjects had a high titre of IgE antibodies to only one of the two toxoids, despite good IgG4 responses to both.

The IgE antibody titres as reported here are underestimated, because clear evidence for interference by non-IgE antibodies (presumably predominantly IgG1 antibodies, but also IgG4 antibodies) was found.

The time course of the IgE antibodies was studied longitudinally in groups B and C, and cross-sectionally in group D. After reaching a peak between 7–14 days after the booster, IgE levels dropped at a variable rate. After 12

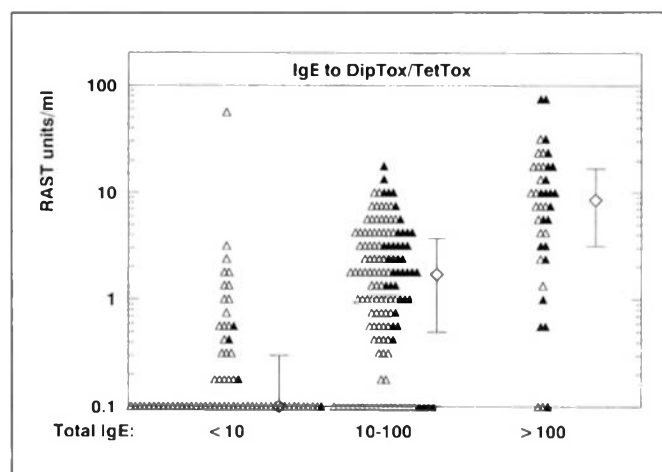


Fig. 1. IgE antibody level to DipTox/TetTox in subjects of group D without IgE antibodies to common inhalant or food allergens [RAST negative (Δ)] compared to subjects with at least one positive RAST ($\blacktriangle$), in relation to the total serum IgE. The error bars indicate the median with the 25th and 75th percentiles.

weeks, the level was approximately 25% of the peak level. In group D, we found no significant change in the percentage positive serum samples or in the value for the 75th percentile for samples obtained between 6 and 300 days. For samples obtained more than 300 days after the booster, the levels were lower, but many positive samples were still found. These results indicate that the IgE response is not short-lived.

No allergic reactions were reported, not even in the two donors who received another booster injection at the time they had a high IgE antitoxoid titre. We considered the possibility that the IgE antibodies were of low avidity, and therefore performed an absorption experiment with solid-phase-coupled TetTox. IgG antibodies were measured by radioimmunoassay using a trace amount of ¹²⁵I-labelled TetTox, to selectively detect high-affinity antibodies. The absorption rate of IgE antibodies was found to be very similar to that of IgG antibodies, which clearly argues against a low avidity of the IgE antibodies. The absence of manifest allergic reactions presumably indicates that blocking IgG antibodies (which are present in relatively high titres) are protective in this situation.

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