

BRIEF COMMUNICATION

Serum basal tryptase may be a good marker for predicting the risk of anaphylaxis in children with food allergy

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Abstract

A relationship between serum basal tryptase (sBT) levels, anaphylactic reactions, and clonal mast cell diseases was shown recently in adults with venom allergy, but the relationship between sBT levels and IgE-mediated food allergy and anaphylaxis is not known. In this study, children with food allergy (FA; $n = 167$) were analyzed in two groups according to the presence (FA+/A+; $n = 79$) or absence of anaphylaxis (FA+/A-; $n = 88$) and were compared with a control group ($n = 113$). Median sBT values in FA+/A+, FA+/A-, and control groups were 4.0 ng/ml (2.8–5.8), 3.6 (2.3–4.5), and 3.3 (2.4–4.4), respectively ($P = 0.022$). sBT measurements higher than the cutoff values of 5.7 and 14.5 were associated with 50% and 90% predicted probabilities, respectively, of moderate to severe anaphylaxis. Children with tree nuts/peanut allergies had significantly higher levels of sBT than children with milk and egg allergy ($P = 0.022$). Results suggest that sBT levels may predict moderate to severe anaphylaxis in children with food allergy, which may follow a particular pattern according to the food allergy phenotype.

Serum basal tryptase (sBT) is used as a marker for mast cell activity in IgE-mediated immune responses and mast cell burden. Tryptase levels increase following mast cell activation, and tryptase is a good marker of systemic anaphylaxis (1). In patients with hymenoptera venom allergy, sBT levels have been associated with the severity of the reactions, and sBT may be a marker for the underlying clonal disease (2–4).

Tryptase is a marker of mast cell involvement in IgE-mediated immune responses. However, the effect of sBT levels on the presence and severity of anaphylaxis in children with food allergy (FA) has not been previously evaluated.

Methods

Study population

The study population consisted of three different groups: children with FA and anaphylaxis (FA+/A+; $n = 79$),

children with FA without anaphylaxis (FA+/A-; $n = 88$), and age- and gender-matched healthy children. The control group consisted of children from whom blood was drawn for routine follow-up or for diagnosis of illnesses not known to induce changes in sBT levels. The study protocol was approved by the Ethical Committee of Hacettepe University.

Diagnosis of food allergy and anaphylaxis

A diagnosis of IgE-mediated FA was established in the presence of all of the following: at least one positive skin prick test; a specific (s)IgE level >0.35 kU/l; a consistent, clear-cut history of an early reaction unequivocally related to the ingestion of food; and positive open challenge tests.

The diagnosis and the severity assessment of anaphylaxis were made according to the recommendations of the EAACI position paper published in 2007 (5).

Study procedures and measurements

Total IgE and sIgE levels, and sBT levels were determined using UniCAP (Pharmacia & Upjohn, Uppsala, Sweden). The detection limit for sBT levels was <1.0 ng/ml. Levels above 11.4 ng/ml were accepted as 'high' according to the

Abbreviations

FA, food allergy; FA+/A+, food allergy with anaphylaxis; FA+/A-, food allergy without anaphylaxis; IQR, interquartile range; sBT, serum basal tryptase.

manufacturer's guide, and children with high levels were investigated in detail for the presence of clonal mast cell disorders and for the presence of heterophile antibodies. Four children with sBT above 11.4 ng/ml (two FA, two healthy) were clinically evaluated for the presence of any dermatological sign of mastocytosis and for clonal mast cell disorders by an experienced pediatric hematologist, and they underwent laboratory investigation for heterophile antibodies (rheumatoid factor and IgA). None of the children had any risk factors or signs of mastocytosis, and they are still under follow-up for early detection of any developing disease.

Statistical analysis

For non-normally distributed data, analyses were performed using the Kruskal–Wallis and Wilcoxon's tests. For sBT that distributed normally, Welch's ANOVA test was performed. To determine the significance of sBT differences across the healthy and FA groups, *P* for trend was calculated using the Jonckheere–Terpstra test. Predicted probability curves were determined using the linear regression model. Logistic regression analysis was performed to detect any factors related to moderate to severe anaphylaxis in children with FA. Factors including age, sBT, eosinophil number, IgE, presence of asthma, allergic rhinitis, atopic dermatitis, and allergy to milk, egg, and peanut or tree nuts were first analyzed in univariate model, and then, multivariate logistic regression analysis was performed with the identified significant variables ($P < 0.05$). SPSS 15.0 software (Chicago, IL, USA) was used for the statistical analyses.

Results

Age and sex distribution of study subjects in three groups as well as laboratory measurements of eosinophil count and total IgE and sBT are provided in Table 1. Median sBT measurements for the healthy, FA+/A–, and FA+/A+ groups were 3.30 ng/ml (IQR: 2.4–4.4), 3.6 (2.3–4.5), and 4.0 (2.8–5.8), respectively ($P = 0.022$). In the comparison of two groups, sBT levels were higher in the FA+/A+ group than in the FA+/A– group ($P = 0.026$), but the significance was lost after Bonferroni correction. In addition, sBT levels were significantly higher in the FA+/A+ group than in healthy group

($P = 0.009$). *P* for trend in the three groups was 0.016 (Fig. 1A).

sBT levels in children with FA were different significantly according to the presence and severity of anaphylaxis ($P = 0.031$). *P* for trend in the four groups was 0.009 (Fig. 1B). sBT level was significantly higher in children with moderate to severe anaphylaxis than in children without anaphylaxis and with mild anaphylaxis in the FA group ($P = 0.004$). Multivariate logistic regression analysis denoted that sBT level was significantly associated with the risk of moderate to severe anaphylaxis in children with FA [OR: 1.3 (1.1–1.5), $P = 0.003$].

Predicted probability curves demonstrated that sBT levels higher than the cutoff values of 5.7 ng/ml and 14.5 were associated with 50% and 90% predicted probabilities, respectively, for moderate to severe anaphylaxis (Fig. 1C).

sBT levels were then analyzed according to the FA phenotype: isolated milk, isolated egg, and finally isolated tree nut/peanut allergies. Children with tree nut/peanut allergies had significantly higher levels of sBT [4.7 (3.0–6.1)] than children with milk [3.4 (2.5–4.3)] or egg allergy [3.8 (2.4–5.5)], $P = 0.022$ (Fig. 1D). The severity of anaphylaxis was significantly different between FA phenotypes ($P = 0.005$), and moderate to severe anaphylaxis was observed more frequently in tree nut/peanut allergy group.

There were no significant correlations between sBT levels and mono-/polysensitization to food, presence of atopic dermatitis, eosinophil counts, total IgE, or age of FA onset.

Discussion

Results of this study suggest that the highest sBT levels are seen in children with FA and anaphylaxis. sBT measurements higher than the cutoff values of 5.7 and 14.5 ng/ml were associated with 50% and 90% predicted probabilities of moderate to severe anaphylaxis, respectively. Children with tree nut/peanut allergies had significantly higher sBT levels than children with milk or egg allergy alone.

The association of elevated sBT levels with anaphylaxis and severity of reactions has only been documented for venom allergic adults (3, 4) and recently, by our group, for venom allergic children (6). Detection of a strong association between severe reactions and higher sBT levels in this study

Table 1 Characteristics of the study population

	Healthy children <i>n</i> = 113	Food allergy without anaphylaxis (FA+/A–) <i>n</i> = 88	Food allergy with anaphylaxis (FA+/A+) <i>n</i> = 79	<i>P</i>
Age (years)*	3.36 (1.94–5.68)	2.48 (1.57–4.52)	2.97 (1.77–5.51)	0.147
Gender: male/female, <i>n</i> (%)	68/45 (60%/40%)	60/28 (68%/32%)	57/22 (72%/28%)	0.199
Eosinophil count (/mm ³)*	200 (100–300)	600 (400–900)	500 (251–922)	<0.001
Total IgE (kU/l)*	24 (7–77)	79 (25–188)	138 (54–400)	<0.001
Family history of allergic disease, <i>n</i> (%)	25 (22.1%)	33 (37.5%)	38 (48.1%)	<0.001
sBT (ng/ml)*	3.30 (2.38–4.36)	3.58 (2.27–4.52)	4.03 (2.84–5.75)	0.022

*Median (interquartile range).

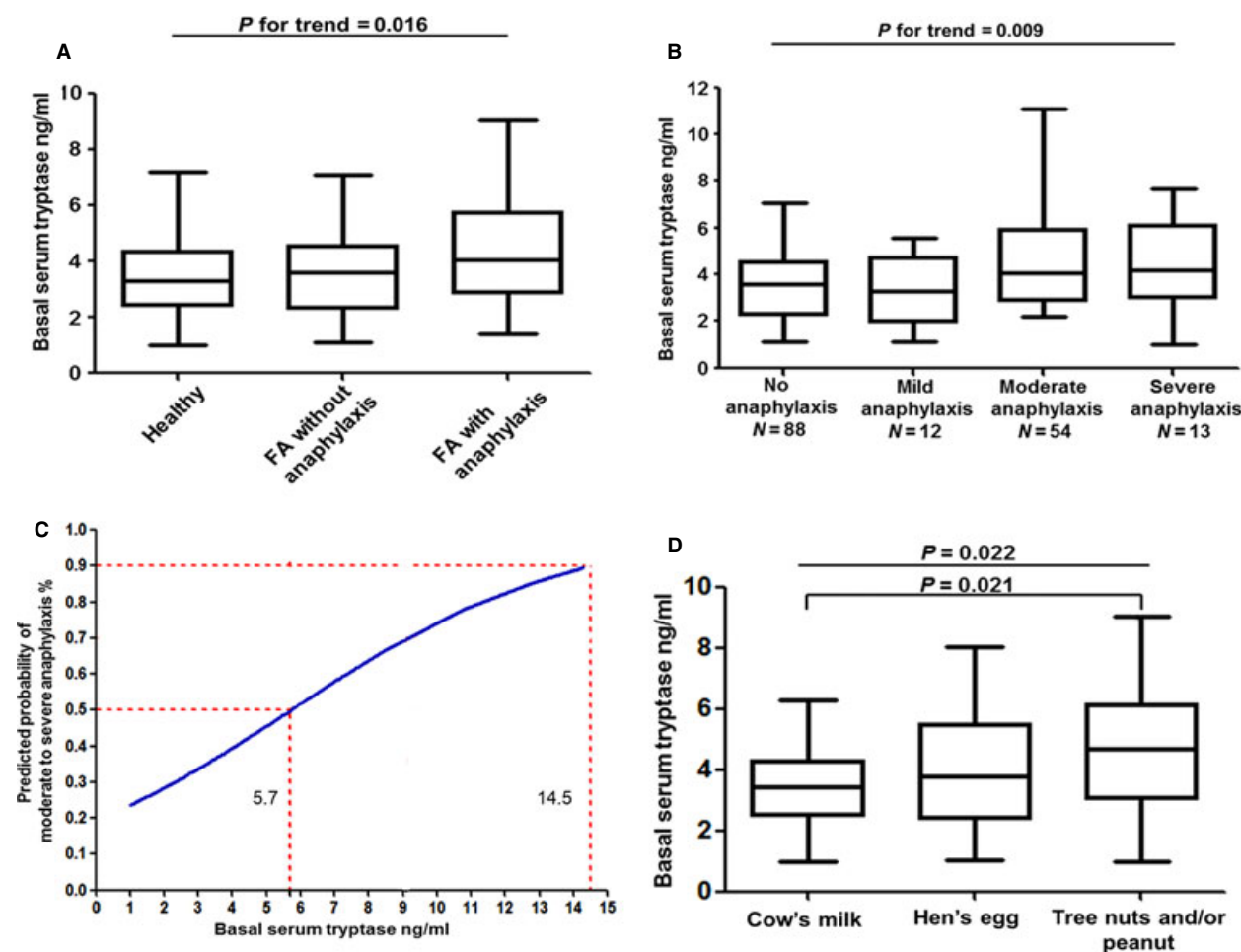


Figure 1 Basal serum tryptase levels (A): between food allergy (FA) with and without anaphylaxis and control groups; (B): in food allergic children according to the anaphylaxis severity; (C): probability of moderate to severe anaphylaxis in children with FA

is consistent with the results of previous studies on patients with venom allergy.

On the other hand, the number of studies concerning the association of sBT with anaphylaxis in patients with food allergy is very limited. Sala-Cunill et al. (7) evaluated 102 anaphylactic adult cases with FA or drug allergy. They concluded that a considerable number of patients did not demonstrate elevated tryptase levels, and more sensitive markers of anaphylaxis are needed.

Bonadonna et al. (4) investigated the relationship between mastocytosis, sBT, and FA. They found that the association between clonal cell disorders and high sBT levels was more likely related to hymenoptera allergy than either food or drug allergy. However, they focused on especially high tryptase levels (>11.4 ng/ml) and mast cell clonal disorders. In another study, Sampson et al. (8) reported two children with severe anaphylaxis and normal tryptase levels. They hypothesized that some anaphylaxis may primarily involve basophils rather than mast cells.

according to serum basal tryptase levels; and (D): basal serum tryptase levels between different FA phenotypes: cow's milk allergy, egg allergy, and tree nuts and/or peanut allergy.

Our study is the first concerning the difference between sBT levels in food allergic children with and without anaphylaxis. Results of this study demonstrated that children with FA and anaphylaxis have highest levels of sBT, when compared to those without anaphylaxis and to healthy children. Statistical differences between groups were small but significant. Recent investigations support the idea that apart from mastocytosis, mast cell numbers, life span, and products were increased in unselected allergic patients even without an allergen exposure (9). These findings increased the importance of sBT in screening patients with allergy to determine high-risk groups, including patients with mast cell activation syndrome (10).

This study is again the first to suggest a predictive cutoff value for the development of moderate to severe anaphylaxis in children with FA. Predictive cutoff values for sBT levels for probability of moderate to severe anaphylaxis would help clinicians to determine high-risk patients. Cardiovascular system symptoms were observed in only three children who had

sBT levels >5.7 ng/ml. Another study by Brockow et al. (11) determined that cardiovascular symptoms were the most frequent symptoms of anaphylaxis in adults with mastocytosis. Our observation is that, even in the absence of mastocytosis, sBT levels >5.7 ng/ml may predispose children with FA to cardiovascular system involvement.

Similar to previous studies, our results suggest no correlation between sBT levels and IgE or eosinophil counts. Poitier et al. (12) showed that patients with high sBT had a low number of cutaneous manifestations, as well as low levels of total IgE and sIgE.

In the literature, foods that most commonly induce severe anaphylaxis and death due to FA are peanuts and tree nuts (13–15). We found that the tree nut/peanut allergy group was associated with significantly higher sBT. In line with the literature, we found that most of the anaphylaxis cases in the peanut/tree nut group had experienced moderate to severe anaphylaxis.

The study has some limitations. First, the population was composed of a specific, selected group of children with IgE-mediated FA, treated at a tertiary care university clinic and, therefore, does not reflect the general population, and the number of severe cases may be higher than expected. Second, FA diagnosis was not based on DBPCFC test, which is the gold standard for FA. However, we believe that the presence of a clear-cut history and positive open food challenge tests, together with the demonstration of sIgE, leaves little doubt for the diagnosis of IgE-mediated FA.

In conclusion, this is the first study to investigate the association between sBT levels and anaphylaxis in children with FA. Our results suggest that sBT levels higher than the cutoff

values may predict moderate to severe anaphylaxis due to FA. Children with tree nut/peanut allergy had significantly higher levels of sBT and had more severe anaphylaxis episodes, as compared with the children with milk and egg allergy.

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Author contributions

UMS and STY contributed to the study design and wrote the article. BB analyzed data and contributed to the discussion. OC and EAY examined the patients, acquired data, performed the required tests, prepared the figures, and contributed to the discussion. AT contributed to the discussion and revised the whole article. CS supervised the whole study concept and design, acquisition of data, analysis, and interpretation, and also critically revised and supervised the manuscript for important intellectual content.

Conflicts of interest

All authors declare no conflicts of interest, and no funding was received for this project.

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