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Basal Serum Tryptase Outperforms Hereditary Alpha Tryptasemia as a Biomarker of Food Allergy Severity

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To the Editor,

Hereditary alpha tryptasemia (HαT) is a genetic trait caused by an increased number of copies of the *TPSAB1* gene, which encodes both alpha(α)- and beta(β)-tryptase and should be suspected when basal serum tryptase (BST) is above 8 μg/L [1, 2]. It has been associated with severity in hymenoptera venom (HVe) allergy [2, 3].

According to our department's clinical care protocol, all anaphylactic patients with baseline serum tryptase (BST) ≥ 8 μg/L are tested for HαT, regardless of the trigger or underlying cause. We analyzed the characteristics of HαT+ patients, and those with food anaphylaxis (FAn) were compared with a FAn cohort with BST < 8 μg/L. The study was approved by the local ethics committee (HCB/2020/1134), and informed consent was waived for this research.

Forty-two patients with anaphylaxis and BST ≥ 8 μg/L were studied and HαT was detected in 29 (69%). Among HαT+ patients, the main anaphylaxis trigger was food (62.1%) followed by drug (20.7%), and HVe accounted for most anaphylaxis in HαT- (38.5% vs. 10.3%). There were no differences in reaction severity or BST, both overall and analyzed by trigger, between HαT+ and HαT-. There was no correlation between the α-tryptase gene copies and BST levels, and all HαT+ presented BST ≥ 9.86 μg/L. Notably, most HαT+(70.4%) had a REMA score < 2 (low risk of clonality) compared to 46.2% of HαT- patients; only 3/29(10.3%) HαT+ was diagnosed with systemic mastocytosis, compared to 3/13 (23.1%) in HαT-. Clinical characteristics of our patients are summarized in Table S1. Finally, among FAn patients, HαT+ had more severe reactions compared to those with FAn and BST < 8 μg/L (oFASS-5 grade 5: 44.4% vs. 26%, $p = 0.094$) (Table 1). Interestingly, when comparing FAn patients with BST ≥ 8 μg/L and < 8 μg/L regardless HαT study, statistically differences were observed (oFASS-5 grade 5: 56.5% vs. 26%) (Table 2).

We found a high prevalence of HαT among anaphylaxis patients with BST ≥ 8, particularly in FAn, where it was associated with severity. Although HαT was only tested in patients with BST ≥ 8 μg/L, the likelihood of finding HαT in patients with BST < 8 seems really low, as described elsewhere [4]. Lyons et al. [2] reported a higher prevalence of HαT in severe HVe anaphylaxis (9.2%-grade IV vs. 4.3%-grade I-III) and a correlation between BST and severity. However, Gonzalez-de-Olano et al. [4] reported similar anaphylaxis severity regardless of HαT status in mast cell activation syndrome (MCAS) patients.

In our series, HαT+ patients were mostly allergic to food, followed by drugs, although previous studies reported [1] drugs or HVe as main culprits. Notably, while the proportion of patients

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TABLE 1 | Comparison of the clinical characteristics of HαT+ and food anaphylaxis patients with BST < 8 μg/L.

Clinical characteristics		HαT+ with FAn; BST > 8 μg/L (*n* = 18)	FAn cohort with BST < 8 μg/L (*n* = 196)	*p*
Gender female: *n* (%)		11 (61.1)	135 (68.9)	0.498
Age (year): mean (SD)		45.39 (39–59)	39.37 (10.18)	0.129
Severity (oFASS-5 classification)	Grade 3: *n* (%)	0 (0)	23 (11.7)	0.229
	Grade 4: *n* (%)	10 (55.6)	122 (62.2)	0.576
	Grade 5: *n* (%)	8 (44.4)	51 (26)	0.094
BST (μg/L): median (Q1–Q3)		15.4 (11.7–18.38)	4.07 (2.99–5.20)	< 0.001*
Total IgE: median (Q1–Q3)		127 (34.9–300)	139 (54.4–306)	0.565

Abbreviations: BST, basal serum tryptase; FAn, food anaphylaxis; oFASS-5, ordinal food allergy severity score with 5 grades.
*Statistically significant difference ($p < 0.05$).

TABLE 2 | Comparison of the clinical characteristics of food anaphylaxis patients with BST > 8 μg/L and BST < 8 μg/L.

Clinical characteristics		FAn; BST > 8 μg/L (*n* = 18)	FAn cohort BST < 8 μg/L (*n* = 196)	*p*
Gender female: *n* (%)		10 (55.6)	135 (68.9)	0.294
Age (year): mean (SD)		48.87 (15.61)	39.35 (10.21)	0.009*
Severity (oFASS-5 classification)	Grade III: *n* (%)	0	23 (11.7)	0.142
	Grade IV: *n* (%)	10 (43.5)	122 (62.2)	0.082
	Grade V: *n* (%)	13 (56.5)	51 (26)	0.002*
BST (μg/L): median (Q1–Q3)		14.3 (10.6–18.3)	4.07 (2.99–5.20)	< 0.001*
Total IgE: median (Q1–Q3)		128 (35.9–399)	139 (54.4–306)	0.830

Abbreviations: BST, basal serum tryptase; FAn, food anaphylaxis; oFASS-5, ordinal food allergy severity score with 5 grades.
*Statistically significant difference ($p < 0.05$).

referred for drug and food allergies to our department is similar (data not shown), HαT+ was predominantly observed in FAn. In this line, Sordi et al. [3] observed that although HVe was the main cause of anaphylaxis in their population, food was most common in HαT+ individuals. Similarly, Gonzalez-de-Olano et al. [4] reported that food as a trigger was significantly more frequent in HαT+(11% vs. 4% HαT-) MCAS patients. Finally, Lang et al. [5] described that having α-tryptase gene copies, compared to only β-tryptase isoforms, was linked to having a history of FAn, aligning with our findings. However, it remained unclear whether this association was related to the presence of germline α-tryptase-encoding sequences [5] or just with BST elevation, as previously reported [6]; although these studies did not include HαT assessment and may be considered a limitation. Our data suggest that the increased severity of FAn is associated with the elevated BST levels, rather than with the presence of HαT per se. This is particularly relevant considering that most patients with BST ≥ 8 μg/L also had HαT+, supporting the role of BST as a useful biomarker of severity regardless of genetic background.

In summary, this is the first report describing the link between severe food anaphylaxis, BST levels, and HαT. Considering that HαT is a trait observed in most anaphylaxis patients with BST > 8 μg/L in our series, and although larger studies are required to understand the modulatory effect of HαT on reactions severity, our results suggest that, at least in food allergy, BST > 8 μg/L may serve as a severity biomarker in those settings where access to genetic study of HαT is limited.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.