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Evaluation of tryptase levels in anaphylaxis

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ABSTRACT

Aims: Tryptase is a serine protease released from mast cells during an acute allergic reaction. Levels of serum tryptase vary among healthy individuals, and there has been a growing debate about the normal and abnormal ranges of tryptase depending on the numbers of mast cells, basal secretion rate, and renal function. To address this point, serum tryptase levels were analyzed in subjects with a prediagnosis or absolute diagnosis of anaphylaxis.

Methods: This was one-centered study performed in a Tertiary Hospital in Turkiye. Patients whose serum tryptase levels were measured between 2020 and 2023 were retrospectively included in this single-center study. Serum tryptase levels that is moment at reaction (RT) and as basal (BT) were analyzed with the same method with ImmunoCAP (Pharmacia, Uppsala, Sweden). The age, gender and reasons for admission of the patients were examined one by one.

Results: Out of approximately 400 test entries, there were valid results of 300. A ratio of 62% of the patients were female (n: 186) and 38% were male (n: 114). The mean age was 18-89 (41.5±14.7)/year. Serum levels of tryptase were measured at the time of reaction in 12.7% of the patients, 4.3% had both reaction and baseline tryptase levels, and the rest had only baseline tryptase analyses. A statistically significant difference was found between the tryptase levels during the reaction in males and females (p: 0.02, female/male: 7.26±4.91/16.93±11.11 µg/L). We found that approximately 90.3% of the patients had serum tryptase levels lower than 11.5 µg/L. There was a statistically significant difference between reaction time (RT) and baseline tryptase (BT) in drug-induced hypersensitivity reactions (p: 0.02), but no difference was found in venom hypersensitivity reactions (p:0.47). There was no correlation between age and tryptase during reaction, but a positive correlation was found between baseline tryptase (p:0.01 r:0.162).

Conclusion: There may be many reasons for high serum tryptase levels. For doctors, it is important to quickly recognize anaphylaxis and manage the treatment process quickly. In this study, we reviewed all tryptase results retrospectively and addressed the etiology of the cases we encountered in our center. We showed that age is a baseline variable in determining tryptase levels. Tryptase can be used as a useful biomarker in diagnosis.

Keywords: Tryptase, anaphylaxis, urticaria, venom, drug

INTRODUCTION

Tryptase is an abundant granule-derived serine protease that is mainly produced by mast cells (MC) and to a much lesser extent by basophils.[1-4] In humans, there are five isoforms as α-, β-, γ-, δ-, and ε-tryptase,[5-7] and precursor forms of α- and β-tryptase are spontaneously secreted by MC during allergic reactions such as anaphylaxis. Mature β-tryptase is retained in secretory granules until its released by activated cells,[9] whereas α-tryptase appears to be processed only to the proform by human MC.[5] Resting MC constitutively secrete monomeric (inactive) pro-tryptase whereas in the case of MC degranulation (e.g. during anaphylaxis), MC release mature tetrameric (active) tryptase.[8,9]

Serum tryptase levels can be measured during the first hours of anaphylaxis, and immunoCAP (Pharmacia, Uppsala, Sweden) measures monomeric and tetrameric forms together (i.e., total serum tryptase) with no subtype specification.[10] Tryptase has proven to be a very useful and specific biomarker to demonstrate MC activation and degranulation during an acute anaphylactic reaction (i.e., within 4 h after the event). Afterwards, a second test after at least 24 h of the allergic reaction to measure baseline value is recommended to make a comparison of tryptase levels. An increase of 20% of basal tryptase levels plus two during the reaction is considered as anaphylaxis.[11-14]

Diagnosis of anaphylaxis is based on suggestive clinical symptoms after exposure to a potential triggering agent which may be supported by in vitro tests.[15] Currently, plasma histamine (or its metabolite, methylhistamine in urine) and total serum tryptase are the only biomarkers available for routine use. The rationale for the use of these mediators for diagnosis is based on the fact that tryptase and histamine contained in MC granules are released upon activation of

the cell. Nowadays, serum tryptase concentration is the most used laboratory test to confirm anaphylaxis. According to current knowledge, tryptase is the best biomarker to assess MC activation. Levels are increased from 15 min to 3 h after anaphylaxis onset.[16,17]

Anaphylaxis is an acute, systemic type 1 hypersensitivity reaction that occurs after re-exposure to an antigen. Anaphylactic reaction is caused by cross-linkage of antigen-specific IgE molecules bound to the surfaces of tissue MC and peripheral blood basophiles, which then undergo degranulation and release a variety of potent mediators including histamine and tryptase. The clinical manifestations of anaphylaxis vary in expression based on immunologic and nonimmunologic factors, which makes a difference in tryptase elevations.[18,19]

A study of postmortem tryptase including 10 anaphylactic deaths found sensitivity of 0.86 and specificity of 0.88 using a 10 µg/L cut-off.[20] Another found tryptase to be elevated in 14/16 anaphylactic deaths (sensitivity 0.88).[21]

A study showed cutoff of tryptase levels at 8.23 ng/ml with a 94.12% sensitivity and 92.31% specificity by using fluoroimmunoassay (UniCAP Tryptase, Pharmacia & Upjohn) in patients with anaphylaxis, whereas the 13.5 ng/ml cutoff recommended by the manufacturers showed 35.29% sensitivity and 92.31% specificity.[22]

Role of Tryptase in Mastocytosis

Mastocytosis results from a clonal, neoplastic proliferation of morphologically and immunophenotypically abnormal MC that accumulate in one or more organ systems. If basal serum tryptase is more than 20 ng/ml, a minor criterion for the diagnosis of systemic mastocytosis is met.[23] MC develop from their uncommitted and MC-committed hematopoietic stem and progenitor cells in the bone marrow and other organs under the influence of stem cell factor, the ligand of the tyrosine kinase receptor KIT.[24]

Recently, elevated tryptase levels in several family members with atypical symptoms of MC activation have been shown to relate to the duplication or triplication of tryptase alpha and beta genes, and it is estimated that 4% to 6% of the general population have increased tryptase gene copy numbers with unclear clinical significance.[25] These patients present baseline and/or acute elevations of MC mediators including tryptase, urinary histamine, and/or prostaglandins.[26]

MC disorders are associated with a greater risk of anaphylaxis. These patients have generally elevated tryptase levels not only during the allergic reaction, but also at baseline. In cases of recurrent unexplained anaphylaxis, elevated basal serum tryptase levels are key to diagnose mastocytosis.[27] Recently, serum tryptase was introduced as an additional diagnostic marker of the disease.[28]

The most common cause of high tryptase value is hereditary alpha tryptasemia (91%), followed by chronic renal failure (7%) and hematological malignancies and mastocytosis (1%).[29] Moreover, obesity can be a cause of elevated tryptase,[30] as well as helminthic infections, hematological malignancies, cardiovascular disease, (nummular) eczema, or rare genetic mutations (e.g., GATA2 or PLAID).[29-31] Even alcohol consumption[32] or tobacco smoking[33] can decrease or elevate serum tryptase, respectively. Also, a case of a patient with Gaucher disease type 1, a lysosomal storage disorder, was reported to have an elevated tryptase level (up to 80 ng/ml) that improved upon initiation of enzyme replacement therapy.[34] Finally, interference with the immunoassay may lead to a false positive result (e.g., by heterophilic antibodies).[35] Tryptase also tends to rise with age.

In Turkiye, the most common causes of anaphylaxis in children are foods, bee venom and drugs;[18] drugs and bee venom in adults.[36] All drugs may potentially cause anaphylaxis. However, nonsteroidal anti-inflammatory agents and betalactam antibiotics are frequently seen.[37,38] When the cause cannot be determined despite all investigations such as measurement of specific IgE levels against potential allergens, skin tests, and detailed clinical evaluation, this is called idiopathic anaphylaxis. Symptoms are the same as those that occur during anaphylaxis with known triggers and may include angioedema, urticaria, tachycardia, pruritus, flushing, dyspnea, wheezing, tachypnea, stridor, dysphagia, hoarseness, nausea, vomiting, diarrhea, syncope, hypotension, and abdominal discomfort. Clinical diagnostic criteria are used for the diagnosis. The World Allergy Organization (WAO) criteria were used for diagnosis. Hypotension/bronchospasm/larynx involvement or acute onset of skin and/or mucosal involvement with respiratory failure or evidence of end-organ damage or severe gastrointestinal symptoms after known or probable allergen exposure.[39]

In a study conducted in our country, the most common culprit drugs were nonsteroidal anti-inflammatory drugs (NSAIDs) (56.9%) and β-lactams (34.7%). The culprit drugs were used parenterally in 13.2% of the patients. Serum basal tryptase value was 3.5 µg/L.[40]

Rationale of this study was that there wasn't many studies about the usefulness of tryptase in phenotyping allergic reactions as anaphylaxis or other immediate type hypersensitivity reactions. Because of this study was to assess the usefulness of tryptase to diagnose anaphylaxis in patients attending the allergic clinic and/or emergency room with clinical symptoms of allergic reaction. Our hypothesis was that tryptase is a useful biomarker in the diagnosis of immediate type hypersensitivity reactions.

METHODS

The study was carried out with the permission of the Kırıkkale University Scientific Researches Evaluation and Ethics Committee (Date: 26.02.2025, Decision No: 2005.02.27). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.This was a retrospective, one-centered study performed. Patient recruitment criteria was that files of patients with tryptase levels between 2020 and 2023 were evaluated in detail. Serum tryptase levels that is moment at reaction (RT) and as basal (BT) were analyzed with the same method with ImmunoCAP (Pharmacia, Uppsala, Sweden).

The age, gender and reasons for admission of the patients were examined one by one. Patients were classified into anaphylaxis, urticaria and control groups according to history and clinic. The diagnosis of "anaphylaxis" was confirmed according to the WAO diagnostic criteria by checking the medical history of patients diagnosed with anaphylaxis. The urticaria group included patients diagnosed with urticaria limited to skin involvement without any other symptoms or organ involvement. The control group included patients with no disease. When the causes of anaphylaxis were examined, they wererecorded in detail as drug, food, bee venom, idiopathic, cold and mastocytosis.

Statistical Analysis

The data was analyzed using SPSS Statistics software (IBM Corp., Armonk, NY, USA). Descriptive statistics, such as numbers and percentages, were used to summarize the demographic and clinical characteristics of the participants. To determine the factors influencing the decision to use tryptase multivariate regression analysis was performed. For the comparison of two groups, the Independent Samples t-test was applied for normally distributed variables, while the Mann-Whitney U test was used for variables that did not show normal distribution. The normality of the data distribution was assessed using the Shapiro-Wilk test. A p-value of less than 0.05 was considered statistically significant in all analyses.

RESULTS

A total of 300 patients were scanned, whose tryptase levels were checked when they applied to the hospital (**Table 1**). A ratio of 62% of the patients were female (n:186) and 38% were male (n:114). The mean age was 18-89 (41.5±14.7)/year. Serum levels of tryptase was measured at the time of reaction in 12.7% of the patients, 4.3% had both reaction and baseline tryptase levels, and the rest had only baseline tryptase analyses. The baseline tryptase levels in women was 3.66±1.95 µg/L, and the baseline tryptase level in men was 3.83±1.19 µg/L (p: 0.053). A statistically significant difference was found between the tryptase levels during the reaction in males and females (p:0.02, female/male: 7.26±4.91/16.93±11.11 µg/L).

Table 1. Demographics of the study group were given

%	All	Anaphylaxis	Urticaria-angioedema	Control
n	300	153	93	54
Age * (min-max)	41.58±14.77 (18-89)	43.70±15.19 (18-89)	40.08±13.87 (19-72)	38.19±14.41 (18-75)
Female, n (%)	186 (62)	86 (56.2)	64 (68.8)	36 (66.7)
Etiology	246			
Drug allergy	91 (36.9)	65 (42.4)	26 (28)	-
Food allergy	15 (6.1)	8 (5.2)	7 (7.5)	-
Venom allergy	64 (26)	49 (32)	15 (16)	-
Idiopathic	65 (26.5)	22 (14.3)	43 (46.2)	-
Cold	5 (2)	4 (2.6)	1 (1.1)	-
Mastocytosis	6 (2.5)	5 (3.2)	1 (1.1)	-

Min: Minimum, Max: Maximum, *:Mean±standard deviation

The ratio of 51% of the applicants were diagnosed with anaphylaxis and 31% with urticaria. In 51 patients presenting with anaphylaxis, tryptase was measured at the time of the reaction with an average of 15.7±14.4 (2.3-75.5) µg/L. There were six patients diagnosed with mastocytosis. The values of baseline tryptase in 262 patients were 4±2.6 (1-183) µg/L. In general, it is seen that the first active agent causing complaints is drugs, followed by venom (**Figure**). The most common drug group was NSAID (n:43, 14.3%). In patients presenting with anaphylaxis, the most common cause was found to be drugs in 42% (n:65). The baseline tryptase levels of those with food allergy (n:15) were 3.20±1.38 (1-6) µg/L. Only one patient had their tryptase measured at the time of the reaction, and the value was found to be 30.6 µg/L.

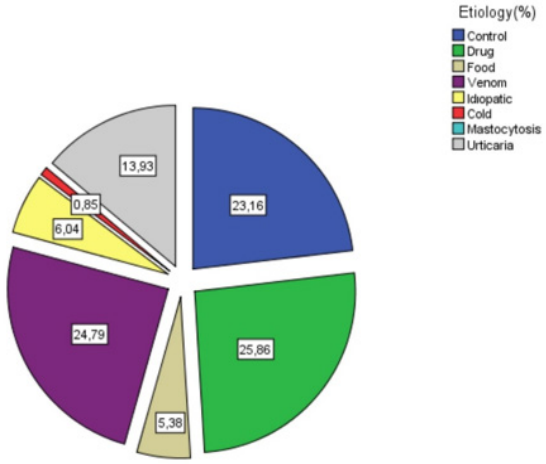

Figure. Rates of reasons in tryptase use during anaphylaxis

We found that approximately 90.3% of the patients had serum tryptase levels lower than 11.5 µg/L. There was a statistically significant difference between RT and BT in drug-induced hypersensitivity reactions (p: 0.02), but no difference was found in venom hypersensitivity reactions (p:0.47) (**Table 2, 3**).

Table 2. Basal and reaction time levels of serum tryptase

Mean±standard deviation (µg/L)	Anaphylaxis (n:153)	Urticaria-angioedema (n:93)	Control (n:54)	p
Basal tryptase	3.06±2.51	3.42±1.79	3.90±2.07	0.27
Reaction time tryptase	14.27±7.12	14.56±5.83	-	0.93

Table 3. Comparison of basal and reaction time tryptase among etiology

Mean±standard deviation (µg/L)	Basal (BT)*	During reaction (RT)*	p
Drug	3.61±1.96	11.92±9.79	0.02
Venom	3.89±2.19	10.74±2.78	0.47

There was no correlation between age and tryptase during reaction, but a positive correlation was found between baseline tryptase (p:0.01 r:0.162). When linear regression analysis was examined between age and reaction, p:0.009 odds ratio [OR]=0.023, confidence interval [CI] 0.06-0.040.

DISCUSSION

The relationship between basal tryptase and age was investigated. It was observed to be approximately 3.3 µg/L between the ages of 10 and 29, followed by a constant increase with age, and the median was found to be 5.4 µg/L after the

age of 70.[41] In our study, the mean basal tryptase was 4±2.6 (1-183) µg/L, and the basal tryptase value increased with increasing age.

Many centers consider the normal range of basal serum tryptase as being <11.4 ng/ml. We found similar baseline tryptase values. However, the use of upper limits of normal ranges as wide-ranging as 8.23 µg/L[22] and 14 µg/L[42] have also been reported. In our research data, RT were <8 µg/L, which may be due to early blood collection.

Recent publications suggest that the global incidence of anaphylaxis ranges from 50 to 112 episodes per 100.000 person-years, with an estimated lifetime prevalence of 0.3–5.1%.[39] A study evaluating 102 anaphylactic adult cases of food allergy or drug allergy concluded that tryptase levels were not increased and that more sensitive markers for anaphylaxis are needed.[43] In our study, when the increase rates in patients were compared from BT to RT, there was an increase of at least 20%+2 µg/L. According to our data, tryptase is a good marker for the diagnosis of anaphylaxis.

Drug-induced anaphylaxis is most commonly triggered by antibiotics and NSAIDs, with age and geographic variation worldwide. Drugs in general are cited as the leading cause of anaphylaxis deaths in adults.[44] NSAI drugs were the primary cause of both presentation and anaphylaxis. In our study, an increase in between BT and RT was found with the drugs, but not with venom. Another study found no association between the severity of NSAID hypersensitivity and elevated baseline serum tryptase levels. The same study also found an association between venom allergy and elevated baseline tryptase levels.[45] The higher baseline tryptase levels in the patients in this study may be due to factors such as different geographic regions and age.

Venom allergy is a typical IgE-mediated reaction because of sensitization to one or more allergens of the venom, and accounts for 1.5-34% of all cases of anaphylaxis.[46] Similarly, in our sample group, there was a 32% rate of venom-induced anaphylaxis applications.

They reported that tryptase levels are rarely elevated in food-induced anaphylaxis.[47,48] This is likely due to localized degranulation rather than general mast cell degranulation. It is thought that the small amount of tryptase entering the circulation is not sufficient to elevate serum levels.[48,49] In our study, we lacked RT data on patients who experienced food-induced anaphylaxis, and the value found in a single patient was elevated. This data contradicts the literature and may be due to the severity of the reaction.

Limitations

To validate our findings, future studies should be conducted with larger sample sizes and populations that have greater diversity in terms of occupation and other relevant factors. One of the limitations of our study is the chronic diseases of the patients and the lack of information on the time of reaction when tryptase was measured.

CONCLUSION

There may be many reasons for high serum tryptase levels. For doctors, it is important to quickly recognize anaphylaxis and manage the treatment process quickly. In this study, we reviewed all tryptase results retrospectively and addressed the etiology of the cases we encountered in our center. We showed that age is a baseline variable in determining tryptase levels. Tryptase can be used as a useful biomarker in diagnosis.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was carried out with the permission of the Kırıkkale University Scientific Researches Evaluation and Ethics Committee (Date: 26.02.2025, Decision No: 2005.02.27).

Informed Consent

Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

The authors declared that this study has received no financial support.

Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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