Tryptase levels in children presenting with anaphylaxis: Temporal trends and associated factors

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Background: The diagnosis of anaphylaxis currently relies on suggestive clinical history after exposure to a potential triggering factor because no reliable diagnostic marker is available to confirm the diagnosis.

Objectives: We aimed to evaluate tryptase levels in children with anaphylaxis and to examine predictors of elevated tryptase level (defined as ≥11.4 μg/L during reaction and for those with a baseline level, defined as a reaction level of at least 2 ng/mL + 1.2 × [postreaction tryptase level]).

Methods: Children presenting with anaphylaxis to the Montreal Children's Hospital were recruited over a 4-year period. Symptoms, triggers, and management of anaphylaxis were documented. Levels during the reaction and approximately 9 months after the reaction were compared on the basis of paired means using the *t* distribution. Multivariate linear and logistic regressions were used to evaluate the association between tryptase levels and risk factors.

Results: Over a 4-year period, 203 children had serum tryptase levels measured. Among these, 39 children (19.2%; 95% CI, 14.1%-25.4%) had elevated levels. Only severe reactions were associated with reaction levels of 11.4 μg/L or more (odds ratio, 6.5; 95% CI, 2.2-19.0). Milk-induced anaphylaxis and severe reactions were more likely associated with increased tryptase levels (beta-adjusted, 4.0; 95% CI, 0.95-7.0, and 7.5; 95% CI, 4.8-10.3, respectively). Reaction levels exceeding the threshold level of 2 ng/mL + 1.2 × (postreaction tryptase level) detected most of the anaphylactic reactions, particularly if baseline levels were taken within 2 months of the reaction.

Conclusions: Tryptase levels are particularly useful for the diagnosis of severe and/or milk-induced anaphylaxis. Assessing the difference between reaction and postreaction tryptase levels may improve diagnostic sensitivity. (J Allergy Clin Immunol 2016;137:1138-42.)

Key words: *Anaphylaxis, children, diagnosis, milk allergy, tryptase*

The diagnosis of anaphylaxis[1,2] currently relies on a suggestive clinical history after exposure to a potential triggering agent or event. However, the diagnosis may be challenging because it is not always possible to identify a clear trigger[2,3] and its presentation may mimic that of other serious medical conditions. Given that anaphylaxis affects at least 1.6% of the North American population,[4] it is crucial to identify biomarkers that will aid in the diagnosis of this important clinical condition.

Certain mast-cell mediators including tryptase, histamine, and platelet-activating factor have been purported to be elevated in anaphylaxis,[5] but practical challenges related to the timing and handling of samples may limit the usefulness of histamine and platelet-activating factor.[2] Tryptase levels within the first 3 hours of anaphylaxis are considered to be a selective marker of anaphylaxis and do not require specific handling of the sample.[6-8] However, large-scale studies establishing its role in anaphylaxis, particularly in pediatrics, are lacking.

We aimed to evaluate tryptase levels in children during and after anaphylaxis and to examine predictors of an elevated reaction tryptase level (defined hereafter as levels ≥11.4 μg/L)[9,10] and an increased difference between reaction and postreaction levels.

METHODS

As part of our Cross-Canada Anaphylaxis Registry, children presenting with anaphylaxis[1] (defined below) to the Montreal Children's Hospital emergency department between April 2011 and April 2015 were recruited. Data on reaction characteristics, triggers, patients' comorbidities, and management were collected either prospectively (at the time of presentation) or retrospectively through chart review as previously described.[11]

Anaphylaxis was defined as involvement of 2 organ systems and/or hypotension in response to a potential allergen,[1] and anaphylaxis severity was classified according to a modified grading system published by Brown.[12] Mild anaphylaxis was characterized by the presence of skin and subcutaneous tissue symptoms (urticaria, erythema, and angioedema) as well as oral pruritus, nausea (ie, gastrointestinal involvement and cutaneous) or nasal congestion, sneezing, rhinorrhea, or throat tightness (ie, respiratory involvement). Moderate anaphylaxis was characterized by the presence of any of the previous symptoms as well as crampy abdominal pain, diarrhea or recurrent vomiting, dyspnea, stridor, cough, wheeze, or "light headedness." Severe anaphylaxis was characterized by cyanosis, hypoxia (saturation <92%), respiratory arrest, hypotension, dysrhythmia, confusion, or loss of consciousness.[12]

Total tryptase levels were measured 30 to 120 minutes after the onset of symptoms at the discretion of the treating physician. All patients with anaphylaxis were referred for assessment and management to the Montreal Children's Hospital Paediatric Allergy clinics. In patients who consented to follow-up by the research team, postreaction tryptase levels were measured

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regardless of the level during anaphylaxis. Total tryptase level was measured using the UniCAP-Tryptase fluoroimmunoassay (Phadia, now Thermo Fisher Scientific, Uppsala, Sweden), following the manufacturer's instructions. A serum tryptase level of more than 11.4 μg/L was considered high.[10] As it has been suggested that the pathognomonic laboratory finding indicative of mast-cell degranulation is an acute total tryptase level (within 4 hours of the reaction) above 2 ng/mL + 1.2 × (baseline tryptase level) (drawn at least 24 hours after resolution of the event),[13,14] we also determined whether the tryptase level drawn during anaphylaxis in our cohort exceeded this threshold.

Descriptive statistics were used to assess demographic, clinical, and reaction characteristics, epinephrine use, and the levels of tryptase during and after the reaction. The demographic, clinical, and reaction characteristics of all participants presenting with anaphylaxis with and without measurement of tryptase levels were compared to address the potential for selection bias. These characteristics were also compared between those with tryptase level measured both during and after the reaction and measured only during the reaction. Tryptase levels during the anaphylactic reaction and postreaction were compared using CIs based on paired means using the *t* distribution. Multivariate logistic regressions were used to identify predictors of an elevated reaction tryptase level (beyond the threshold of 11.4 μg/L) as well as a reaction tryptase level exceeding the threshold of 2 ng/mL + 1.2 × (baseline tryptase level). Multivariate linear regressions were used to identify predictors of level of tryptase during the reaction and differences between tryptase levels during and after the reaction. Potential predictors included age, sex, reaction trigger, reaction severity, history of atopy, and interval between measurement of reaction and postreaction tryptase level (where applicable). All statistical analyses were conducted using R version 2.12.0 (October 15, 2010).

This study received ethics approval from the McGill Research Ethics Board.

RESULTS

Patient characteristics, anaphylaxis severity, management, and triggers

Over a period of 4 years, 965 children presented to the emergency department with anaphylaxis and of these, 203 had serum tryptase levels measured within 2 hours of the onset of the anaphylactic reaction. The 203 children with measurement of tryptase level were compared with the 762 children who were admitted to the emergency department with anaphylaxis over the same time period without measurement of tryptase level (Table I). The 2 groups were comparable regarding age, sex (predominantly male), reaction triggers, and known asthma. Most of the reactions occurred at home and during normal activity. In contrast, there were more children recruited prospectively who had tryptase level measured. Although food was the major trigger in both groups, tree nut was a more common precipitant in the group with tryptase level measurements. Although eczema was more commonly reported in children with tryptase level measurements, a known food allergy was more commonly reported in children without tryptase level measurements. Severe reactions were reported more frequently in children with tryptase level measurements, and the use of epinephrine inside the hospital was also higher in participants with tryptase level measurements, but the use outside the hospital was lower.

Serum tryptase level concentrations

Among the 203 children with serum tryptase level measurements, the mean level was 7.6 ± 6.2 μg/L and 39 cases (19.2%; 95% CI, 14.1% to 25.4%) had elevated tryptase levels (≥11.4 μg/L). Elevated levels were found in 9 of 18 or 50.0% (95% CI, 29.0% to 71.0%) of severe reactions, in 24 of 148 (95% CI, 10.8% to 23.4%) or 16.2% of moderate reactions, and in 6 of 37 or 16.2% (95% CI, 6.8% to 32.7 %) of mild reactions.

Among the 203 cases with tryptase level measurements within 2 hours of reaction, postreaction tryptase level was available on 68 (33.5%; 95% CI, 27.1% to 50.5%). The mean time interval between postreaction and reaction levels was 8.7 months. Tryptase levels during reaction were higher in subjects with postreaction levels. Other patient and reaction characteristics were comparable between those with and without postreaction levels (Table II). Most were recruited prospectively and were male. Most reactions were triggered by food and occurred most commonly at home and during normal activity.

Of the 68 children with postreaction tryptase levels, the mean tryptase level was 9.9 μg/L at the time of reaction and 3.6 μg/L postreaction, yielding a difference of 6.3 μg/L (95% CI, 4.7-7.8). The suspected trigger was confirmed in 76.5% (95% CI, 69.9% to 82.3%) of the 203 children who had reaction tryptase level measured and in all cases who had both reaction and postreaction measurements. In 41 of 68 children (60.3%; 95% CI, 47.7% to 71.7%), the reaction tryptase level exceeded the published threshold of 2 ng/mL + 1.2 × (baseline or postreaction tryptase level). Levels exceeding this threshold were found in 85.7% of severe reactions (95% CI, 42.0% to 99.2%), 54.2% of moderate reactions (95% CI, 39.3% to 68.4%), and 69.2% (95% CI, 38.9% to 89.6%) of mild reactions.

Specific risk factors associated with elevated tryptase level

The presence of a severe reaction was the only factor associated with elevated tryptase levels (≥11.4 μg/L) during the reaction, after adjusting for sociodemographic and reaction characteristics and comorbidities (adjusted odds ratio, 8.0; 95% CI, 5.2-10.8). A severe reaction and a milk trigger were associated with increased levels of tryptase during the reaction, regardless of previously published thresholds (beta-adjusted, 7.5; 95% CI, 4.8-10.3, and 4.0; 95% CI, 0.95-7.0, respectively). A severe reaction was also associated with an increased difference between reaction and postreaction tryptase levels (beta-adjusted, 9.7; 95% CI, 5.6-13.8). Interestingly, measurement of tryptase levels at least 3 months after the reaction was associated with a decreased difference (beta-adjusted, −3.7; 95% CI, −6.9 to −0.4).

The reaction tryptase levels was more likely to exceed 2 ng/mL + 1.2 × (baseline tryptase level) in severe reactions (adjusted odds ratio, 1.5; 95% CI, 1.1-2.1), whereas it was less likely to exceed this threshold with an increased time interval between reaction and postreaction levels (adjusted odds ratio, 0.99; 95% CI, 0.98-0.99). We did not detect a significant interaction between the type of food trigger (including milk) and age.

DISCUSSION

We have conducted the largest study assessing levels of tryptase during and after anaphylaxis in children and the first study to evaluate factors associated with an elevated level or a difference between postreaction and reaction levels. Our results reveal that the tryptase level during the reaction exceeded a previously published threshold in 50% cases of

TABLE I. Sociodemographic and clinical characteristics of children with and without tryptase level measurements

Characteristic	Tryptase level taken within 2 h of reaction, % (95% CI)* (N = 203)	No tryptase level taken, % (95% CI)* (N = 762)	Difference, % (95% CI)
Prospective reactions†	80.8 (74.5-85.8)	37.4 (34.0-41.0)	43.4 (36.7-50.1)
Age (y), median (IQR)	5.2 (1.7-12.2)	5.9 (2.5-11.5)	−0.2 (−1.1 to 0.7)
Mean ± SD	7.1 ± 5.6	7.3 ± 5.4	
Sex: male	57.6 (50.5-64.5)	57.3 (53.7-60.9)	0.3 (−7.7 to 8.2)
Food trigger	80.8 (74.5-85.8)	83.2 (80.3-85.7)	−2.4 (−8.8 to 3.9)
Food-induced reaction triggered by tree nuts	22.3 (16.2-29.8)	11.2 (9.0-14.0)	11.1 (3.7-18.5)
Food-induced reaction triggered by peanuts	19.1 (13.4-26.3)	22.9 (19.7-26.4)	−3.8 (−11.1 to 3.6)
Food-induced reaction triggered by milk	9.6 (5.6-15.5)	6.0 (4.3-8.2)	3.6 (−1.8 to 8.9)
Venom trigger	2.0 (0.6-5.3)	2.0 (1.1-3.3)	0.001 (−2.2 to 2.2)
Drug trigger	5.9 (3.2-10.3)	2.8 (1.7-4.3)	3.2 (−0.6 to 6.9)
Unknown trigger	9.8 (6.3-15.0)	9.7 (7.5-12.1)	0.1 (−4.6 to 4.9)
Other trigger	4.9 (2.5-9.1)	2.4 (1.4-3.8)	2.6 (−0.9 to 6.0)
Reaction at home	61.7 (54.3-68.6)	51.2 (47.2-55.3)	10.4 (2.1-18.8)
Reaction not during exercise	84.8 (78.3-89.7)	82.0 (78.3-85.2)	2.8 (−4.0 to 9.5)
Known food allergy	32.8 (26.5-39.6)	53.2 (49.6-56.9)	−20.4 (−28.1 to −12.7)
Known asthma	21.9 (16.5-28.4)	18.3 (15.6-21.3)	3.6 (−3.1 to 10.3)
Known eczema	8.5 (5.2-13.4)	3.2 (2.1-4.8)	5.2 (0.9-9.6)
Severe anaphylaxis	8.9 (5.5-13.9)	3.0 (2.0-4.6)	5.8 (1.4-10.3)
Moderate anaphylaxis	72.9 (66.2-78.8)	72.4 (69.1-75.6)	0.5 (−6.7 to 7.7)
Epinephrine administered inside hospital	65.5 (58.5-71.9)	39.4 (36.0-43.0)	26.1 (18.4-33.8)
Epinephrine administered outside hospital	23.6 (18.1-30.2)	34.1 (30.8-37.6)	−10.5 (−17.5 to 3.4)

IQR, Interquartile range.
*Estimates for all variables are presented in percentage unless otherwise indicated.
†This term was used when data were collected at the time of patient presentation to the emergency department and not through retrospective chart review.

severe anaphylaxis and in only 16.2% cases of mild or moderate anaphylaxis. Hence, it has a poor sensitivity in the diagnosis of mild and moderate reactions although it may be helpful in severe reactions in which the diagnosis of anaphylaxis is unclear, for example, when a specific trigger is not identified. Studies conducted in adults have also reported an association between anaphylaxis severity and elevated tryptase level.[5,15,16] Hence, tryptase level may help distinguish anaphylaxis from other life-threatening conditions with a similar presentation, such as cardiogenic or septic shock, regardless of a patient's age. Establishing a correct diagnosis remains important because life-saving secondary prevention measures (eg, carrying an epinephrine autoinjector) can then be recommended.

The poor sensitivity of an elevated tryptase level, particularly in cases of mild and moderate anaphylaxis, is in line with previous smaller studies conducted in adults.[5,9] To enhance the sensitivity of tryptase level measurements, several approaches have been advanced in the literature, mainly based on the comparison with tryptase level measured postreaction,[7,17] and several recommend serial tryptase level measurements.[18] Given that measurements of level of mature tryptase stored in mast cells (and secreted only during mast-cell activation) are not widely available, an accepted approach is based on the detection of an elevated level of tryptase during the reaction of at least 2 ng/mL + 1.2 × (postreaction or baseline tryptase level).[13,14] Indeed, most of the cases in our study (with postreaction tryptase level measurements) had reactions levels exceeding the proposed threshold (60.3% of the cases; 95% CI, 47.7% to 71.7%), especially in severe reactions in which 85.7% of the cases (95% CI, 42.0% to 99.2%) had an elevated tryptase level.

Others defined a threshold as a difference of 2.0 μg/L or more based on sting challenges during venom immunotherapy.[18] In a study of 127 cases presenting with anaphylaxis, a difference between reaction and postreaction levels (drawn within 90 minutes of reaction) of at least 2.0 μg/L occurred in 53% of those with mild skin-only reactions, 58% with moderate anaphylaxis (using a grading system comparable to the one used in this article), and 84% with severe anaphylaxis.[19] Similarly, we detected a difference of at least 2.0 μg/L in 85.7% (95% CI, 42.0% to 99.2%), 62.5% (95% CI, 47.3% to 75.7%), and 76.9% (95% CI, 46.0% to 93.8%) of children with severe, moderate, and mild anaphylaxis, respectively.

The association between a milk trigger and increased tryptase levels is a unique finding of our study. These results suggest that tryptase level may be a useful diagnostic tool for anaphylaxis presenting in infancy when milk is often the first potential food allergen introduced. The differential diagnosis of anaphylaxis might be especially challenging in this age group because of limited verbal communication, the presence of masquerading conditions such as food protein–induced enterocolitis syndrome[20] and viral infections, and the usual introduction of cow's milk formula in the first year of life.[21] We postulate that exposure to cow's milk formula/milk may involve larger quantities of allergen because it is usually in a liquid form.

In contrast to other studies, ours is the first study to evaluate tryptase levels over a period of several months up to almost 5 years (Table II) after the reaction has occurred. Our results suggest that reaction and postreaction levels of tryptase are likely to differ more if the postreaction levels are measured within the first 2 months. Our observation that at intervals of 3 months or more between reaction and postreaction measurements, the difference

TABLE II. Characteristics of patients with tryptase levels taken during reaction and postreaction versus patients with no postreaction levels

Characteristic	Tryptase level taken within 2 h of reaction and postreaction levels, %* (95% CI) (N = 68)	Tryptase level taken within 2 h of reaction and no postreaction levels, % (95% CI) (N = 135)	Difference, % (95% CI)
Prospective reactions†	86.8 (75.9-93.4)	77.8 (69.7-84.3)	9.0 (−2.8 to 20.8)
Age (y), median (IQR)	5.7 (1.7-12.3)	5.1 (1.8-11.8)	0.4 (−1.3 to 2.1)
Mean ± SD	7.3 ± 5.7	6.9 ± 5.5	
Time interval between baseline and reaction levels (mo), Median (IQR)	2.8 (1.3-10.0)		
Range	0.1-64.8		
Sex: Male	57.4 (44.8-69.1)	57.8 (49.0-66.1)	−0.4 (−15.3 to 14.4)
Food trigger	80.9 (69.2-89.0)	75.6 (67.3-82.4)	5.3 (−7.6 to 18.3)
Food-induced reactions triggered by tree nuts	23.6 (13.6-37.3)	21.0 (13.9-30.2)	2.7 (−12.4 to 17.7)
Food-induced reactions triggered by peanut	12.7 (5.7-25.1)	21.9 (14.7-31.2)	−9.2 (−22.4 to 4.0)
Food-induced reactions triggered by milk	10.9 (4.5-22.9)	8.6 (4.2-16.1)	2.4 (−8.9 to 13.5)
Venom trigger	1.5 (0.1-9.0)	2.2 (0.6-6.9)	−0.8 (−5.3 to 3.8)
Drug trigger	2.9 (0.5-11.2)	7.4 (3.8-13.6)	−4.5 (−11.5 to 2.6)
Trigger unknown	8.8 (3.6-18.9)	10.4 (6.0-17.1)	−1.5 (−11.1 to 8.0)
Other trigger	5.9 (1.9-15.1)	4.4 (1.8-9.8)	1.4 (−6.3 to 9.1)
Reaction at home	68.2 (55.4-78.8)	58.2 (48.9-67.0)	10.0 (−5.4 to 25.4)
Reaction not during exercise	87.9 (76.1-94.6)	83.2 (74.7-89.3)	4.7 (−7.4 to 16.9)
Known food allergy	31.3 (20.9-44.0)	33.6 (25.8-42.3)	−2.2 (−17.0 to 12.6)
Known asthma	25.4 (15.9-37.7)	20.1 (13.9-28.1)	5.2 (−8.3 to 18.8)
Known eczema	11.9 (5.7-22.7)	6.7 (3.3-12.7)	5.2 (−04.7 to 15.2)
Severe reaction	10.3 (4.6-20.7)	8.1 (4.3-14.4)	2.1 (−7.5 to 11.8)
Moderate reaction	70.6 (58.1-80.7)	74.1 (65.7-81.1)	−3.5 (−17.7 to 10.7)
Epinephrine administered intramuscularly inside hospital	66.2 (53.6-76.9)	65.2 (56.4-73.0)	1.0 (−13.8 to 15.8)
Epinephrine administered intramuscularly outside hospital	25.0 (15.6-37.2)	23.0 (16.4-31.1)	2.0 (−11.6 to 15.6)
Elevated tryptase level (≥11.4 μg/L)	25.0 (15.6-37.2)	16.3 (10.7-23.9)	9.7 (−4.4 to 21.8)
Tryptase level during reaction (μg/L), mean ± SD	9.9 ± 6.6	7.1 ± 5.6	2.8 (0.9-4.7)
Tryptase level postreaction (μg/L), mean ± SD	3.6 ± 1.8		

IQR, Interquartile range.
*Estimates are percentages unless otherwise indicated.
†This term was used when data were collected at the time of patient presentation to the emergency department and not through retrospective chart review.

is likely to decrease has practical implications for the diagnosis of anaphylaxis. In line with this observation, we found that the reaction tryptase level was more likely to exceed the threshold of 2 ng/mL + 1.2 × (postreaction tryptase level) when we restricted our analysis to the 31 children who had their postreaction tryptase level measured within the first 2 months after presenting with anaphylaxis. In these children, the difference exceeded the threshold in 100% (95% CI, 46.3% to 100%) of severe and 80.0% (95% CI, 29.9% to 98.9%) of mild reactions. Similarly the sensitivity of the absolute difference of at least 2 μg/L increased to 100.0% (95% CI, 46.3% to 100.0%) and 80.0% (95% CI, 29.9% to 98.9%) of severe and mild reactions, respectively. However, the sensitivity decreased for moderate reactions for both methods (52.4%; 95% CI, 30.3% to 73.6%, and 57.1%; 95% CI, 34.4% to 77.4%, respectively).

Our study has some potential limitations. Given that children who had tryptase levels measured were more likely to have severe reactions, and given the association between reaction severity and tryptase levels, it is likely that a lower percentage would have had an elevated tryptase level had all participated. In addition, only 68 patients had measurements during and after the reaction. Nevertheless, our results are consistent with results of previous studies, suggesting that a tryptase level during reaction exceeding the threshold level of 2 ng/mL + 1.2 × (postreaction tryptase level) or a difference of 2.0 μg/L between reaction and postreaction levels will detect most of the anaphylaxis reactions, particularly if measured within 2 months of the anaphylactic reaction. Although a higher percentage of the group with tryptase levels had a tree-nut allergy and eczema and a lower percentage had a known food allergy, these are not likely to affect tryptase levels.

In conclusion, our results do not support the use of total tryptase level as a sole diagnostic marker in children at the time of anaphylaxis because it exceeds published thresholds in only a minority of cases. However, it may be useful in establishing the diagnosis in severe cases, especially milk-induced anaphylaxis, and when compared with postreaction levels. In addition, we have demonstrated that tryptase reaction levels exceeding the threshold of 2 ng/mL + 1.2 × (postreaction tryptase level) may be very useful in establishing the diagnosis of anaphylaxis. Hence, we anticipate that drawing a tryptase level both during and shortly after an episode of anaphylaxis may contribute to higher sensitivity of anaphylaxis diagnosis regardless of its trigger. Future studies assessing the difference between reaction and postreaction levels in larger samples and assessing the validity of other diagnostic tools in pediatric anaphylaxis such as prostaglandin D2,[22] chymase, and carboxypeptidase A3[23] are required to improve the diagnosis of anaphylaxis.

Clinical implications: Serum tryptase levels may be useful in establishing the diagnosis of severe/milk-induced anaphylaxis and when compared with postreaction levels drawn within 2 months of the reaction.

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