Allergol Immunopathol (Madr). 2014;42(6):544–552

Allergologia et immunopathologia

Sociedad Española de Inmunología Clínica, Alergología y Asma Pediátrica

www.elsevier.es/ai

ORIGINAL ARTICLE

Clinical characteristics and risk profile of patients with elevated baseline serum tryptase

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Received 9 December 2013; accepted 25 May 2014
Available online 12 September 2014

KEYWORDS
Basal serum tryptase;
Mast cell activation syndrome;
Mastocytosis;
Anaphylaxis

Abstract
Background: The clinical relevance of elevated basal serum tryptase (eBST ≥ 11.4 ng/ml) often remains unclear.
Methods: BST was assessed in 15,298 patients attending our outpatient clinic. Frequency and severity of anaphylaxis was compared in 900 patients with eBST and 900 patients with normal BST. The prevalence of eBST was evaluated in patients with drug reactions, urticaria, gastrointestinal symptoms or venom allergy. Mast cell-associated symptoms were recorded prospectively in 100 patients with eBST and 100 controls using a standardised questionnaire.
Results: 5.9% ($n = 900$) of 15,298 patients had eBST ≥11.4 ng/ml (mean 20 ± 21 ng/ml, 11.4–390 ng/ml). In 47% of them BST was <15.0 and in 78% <20.0 ng/ml. In patients with normal BST (4.5 ± 2.1 ng/ml), mean levels increased continuously with age (0.28 ng/ml per decade; $p < 0.001$). Fatigue, meteorism, muscle/bone ache, vertigo, tachycardia, flush, palpitations, diarrhoea and oedema were associated with eBST ($p < 0.05$ to <0.0001) without significant differences between slightly (11.4–20 ng/ml) or strongly (>20 ng/ml) eBST. eBST was significantly associated with adverse reactions to drugs (34%), radio contrast media (15%) and insect stings (24%) ($p < 0.05$). Anaphylaxis was more common in patients with eBST (21% vs. 14%, $p < 0.001$). The relative role of insect stings, drugs and food as the most important triggers was similar in patients with elevated and normal BST. Severe reactions (grade 3/4) occurred most often in subjects with BST >20 ng/ml (BST <11.4 mg/ml: 2.8%; 11.5–20 ng/ml: 5.9%; >20 ng/ml: 12.4%).
Conclusions: In clinical practice it appears reasonable to assess BST, besides after anaphylactic reactions also in patients suffering repeatedly from vertigo, flush, tachycardia, palpitations, oedema and nausea. Even patients with slightly eBST have a higher risk of anaphylaxis and experience more severe reactions.

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http://dx.doi.org/10.1016/j.aller.2014.05.002

Introduction

Assessment of basal serum tryptase (BST) is part of the routine diagnostic work-up after anaphylactic reactions to insect stings.[1–3] BST values exceeding 20 ng/ml are not only associated with an elevated risk for anaphylaxis[4,5] but represent a minor criterion for mastocytosis.[6] However, the clinical relevance and the risk profile of slightly elevated BST values ranging between the cut off level 11.4 ng/ml and 20 ng/ml are still unclear. In patients with Hymenoptera venom allergy, an elevated risk for severe anaphylactic reactions has been proposed starting with a BST as low as 5 ng/ml, a value far below the cut off of 11.4 ng/ml.[7]

There is a lack of cardinal symptoms helping to diagnose mastocytosis or mast cell activation syndromes. This may be mostly explained by the heterogeneous and unspecific symptomatology of these diseases. Only cutaneous mastocytosis with its characteristic Darier's sign can be easily diagnosed clinically. On the other hand, episodic cutaneous symptoms such as flushing, pruritus or urticaria, abdominal complaints with nausea, diarrhoea and cramps as well as cardiovascular symptoms such as hypotension or tachycardia are characteristically found in patients with mast cell diseases.[4,8,9] These symptoms, especially when occurring repeatedly and/or simultaneously, should give reason to assess BST.

The most common commercially available testing kit for tryptase (Thermo Fisher Scientific, Uppsala, Sweden) measures alpha as well as beta tryptase (''total'' tryptase).[10] Immature precursors of alpha and beta tryptase are continuously released into the circulation giving a gross estimate on the bodies mast cell load. However, only mature beta tryptase is released in the course of IgE- and non-IgE-mediated mast cell degranulation. Currently, a selective commercial assay for mature beta tryptase is not available, therefore the recent literature has been focusing on ''total serum tryptase''.

The aims of this study were to explore the frequency of elevated BST among routine ''allergy'' patients of a large outpatient allergy clinic and their distribution with respect to age and gender. In addition, symptoms in patients with elevated BST were assessed in a prospective as well as retrospective manner in order to identify cardinal symptoms helpful in detecting patients with mast cell diseases. Finally, the clinical relevance of slightly (11.4–20 ng/ml) and strongly (>20 ng/ml) elevated BST levels with respect to the risk profile of patients (including anaphylaxis) was evaluated.

Materials and methods

This manuscript consists of a retrospective and a prospective part. Table 1 gives an overview of all patient groups investigated.

Patients and BST assessment

From 2004 to 2012 BST was assessed in a total of 15,298 patients (5112 male, 10,186 female, mean age 52.2 ± 18.5 years, range 1–99 years). In case of multiple assessments in one patient, the very first value was used. Data were analysed with regard to gender, age and frequency of elevated BST values. The cut-off level for elevated tryptase was 11.4 ng/ml following the recommendations of the manufacturer.

Anaphylaxis and risk assessment

The frequency and severity of anaphylactic reactions was analysed in 900 patients with elevated BST and 900 randomly chosen patients with normal BST. Reactions were counted as anaphylactic only when having appeared immediately (i.e. within 15 min) after a possible causative event and when other causes have been ruled out. Anaphylactic reactions were graded according to Ring and Messmer.[11]

Prevalence of elevated BST in patients with specific symptoms

In order to assess the prevalence of elevated BST in certain clinical conditions, 100 consecutive patients each with specific symptoms such as (1) drug intolerance; (2) recurrent gastrointestinal symptoms (diarrhoea, meteorism, abdominal cramps); (3) multilocular symptoms (2–3 different symptoms such as diarrhoea, abdominal cramps, debilitating fatigue, headache, vertigo, muscle and bone ache); or (4) chronic-recurrent urticaria, were analysed.

In a retrospective analysis, 248 consecutive patients with Hymenoptera venom allergy experiencing local swellings or systemic reactions after an insect sting were analysed to evaluate the frequency of elevated BST levels and their distribution in regard to the severity of the sting reaction. Furthermore, 63 venom-allergic patients with elevated BST were selected to study the relationship between severity of the sting reaction and the magnitude of the elevated BST level.

Clinical characterisation of patients with elevated BST

From January until October 2012, potentially mast cell-associated symptoms were assessed in 100 patients with elevated BST (≥11.4 ng/ml) using a detailed, standardised questionnaire. All patients signed a written informed consent. BST had been assessed initially because of cutaneous symptoms (urticaria, flush, pruritus, oedema; $n = 28$), recurrent diarrhoea and other gastrointestinal symptoms ($n = 26$), adverse drug reactions ($n = 23$) or reactions after insect stings ($n = 11$). In a few cases, anaphylactic reactions, hypotension or headache had led to BST assessment. Four patients already suffered from a known cutaneous or indolent systemic mastocytosis. A control group consisted of 100 age- and gender-matched persons with allergic rhinoconjunctivitis. In order to avoid any systematic error when comparing the prevalence of particular symptoms in patients and controls, the initial symptoms having led to the first BST assessment were not considered.

Items of the questionnaire covered symptoms regarding the skin, gastrointestinal tract, respiratory tract and cardiovascular system as well as psychological and the general condition. In order to be eligible for inclusion to the study,