

# Tryptase, a diagnostic marker in suspected mastocytosis

Mastocytosis

# Mastocytosis – a disease with many faces

Mastocytosis is a rare condition. However, the suspicion of the disease and the need for evaluation of a possible mastocytosis is common. There are different forms of mastocytosis, such as systemic mastocytosis (SM) and cutaneous mastocytosis (CM).<sup>1-9</sup>

How can your patient with a suspected mastocytosis benefit from tryptase measurement?

Tryptase baseline levels reflect the mast cell burden in the body. Together with clinical findings, ImmunoCAP™ Tryptase test results can help to:

- rule in SM
- rule out SM

# How is mastocytosis diagnosed?

Mastocytosis is characterized by increased numbers of mast cells in different organs. The baseline level of tryptase in the circulation reflects the number of mast cells. There are different forms of mastocytosis.

## Systemic mastocytosis

SM that involves several organs is more severe and more prevalent in adults than in children. Many different symptoms may appear and they often include skin lesions. Also, many diffuse symptoms occur, such as: pain in inner organs, bone pain, diarrhea and vomiting, weight loss, and cardiovascular symptoms. Tryptase levels are increased in the majority of various kinds of SM.<sup>1-5</sup>

## Cutaneous mastocytosis

CM that involves only skin symptoms is more common in children than adults, often benign, often outgrown, and tryptase levels are usually within normal range.<sup>1-5</sup> In CM, tryptase levels are usually normal to slightly elevated.<sup>1</sup>

## Definitions of mastocytosis and diagnostic criteria

The World Health Organization (WHO) has a consensus on definitions of various forms of mastocytosis and on diagnostic criteria.<sup>1</sup> The classification includes major and minor diagnostic criteria for SM. A persistently elevated baseline serum tryptase value above 20 µg/l (1 µg/l = 1 ng/ml) is one minor criterion.<sup>1</sup>

A tryptase test is often used as an initial test.

## WHO diagnostic criteria for systemic mastocytosis<sup>1,5</sup>

### Diagnosis of SM

Major criterion + at least 1 minor criterion, or at least 3 minor criteria.

#### • Major criterion

- Multifocal dense infiltrates of mast cells (≥15 mast cells in aggregates) detected in sections of bone marrow and/or other extracutaneous organ(s).

#### • Minor criteria

- In biopsy sections of bone marrow or other extracutaneous organs, >25% of the mast cells in the infiltrate are spindle-shaped or have atypical morphology or >25% of all mast cells in bone marrow aspirate smears are immature or atypical.
- Detection of an activating point mutation at codon 816 of *KIT* in the bone marrow, blood, or another extracutaneous organ.
- Mast cells in bone marrow, blood, or another extracutaneous organ express CD25, with or without CD2, in addition to normal mast cell markers.
- Serum total tryptase is persistently >20 ng/mL, unless there is an associated myeloid neoplasm, in which case this parameter is not valid.

# How can a tryptase test help?

Example: A patient has a history of repeated anaphylaxis after insect stings, and is considered for venom immunotherapy (VIT)

## **Transient increase of tryptase during a severe reaction helps to confirm mast cell activation as the cause of anaphylaxis**

This patient repeatedly had confirmed anaphylaxis due to mast cell activation, a confirmed IgE-mediated allergy to wasp and bee venoms, and was proposed for VIT. Baseline tryptase was persistently at 40 µg/l (i.e., >20 µg/l), and a possible SM was evaluated by a specialist before start of VIT.

## **Tryptase helps to rule in systemic mastocytosis and guide VIT treatment**

In this patient example, one major and one minor criterion were fulfilled and consistent with clinical finding. The specialist made the diagnosis of SM.

A persistently elevated baseline serum tryptase value above 20 µg/l is one minor criterion of SM, according to WHO diagnostic criteria.<sup>1</sup> A bone marrow biopsy provides the major diagnostic criterion.

There is a consensus among leading allergy organizations that SM is a risk factor for anaphylaxis<sup>5,10-12</sup> and that venom-allergic patients with SM should receive life long VIT.

In SM, tryptase levels are most often increased, but may be normal. In CM, the diagnosis criteria for SM are not fulfilled, however, one or two minor diagnostic criteria for SM may present, such as an elevated tryptase level.<sup>1</sup>



# How can a tryptase test help?

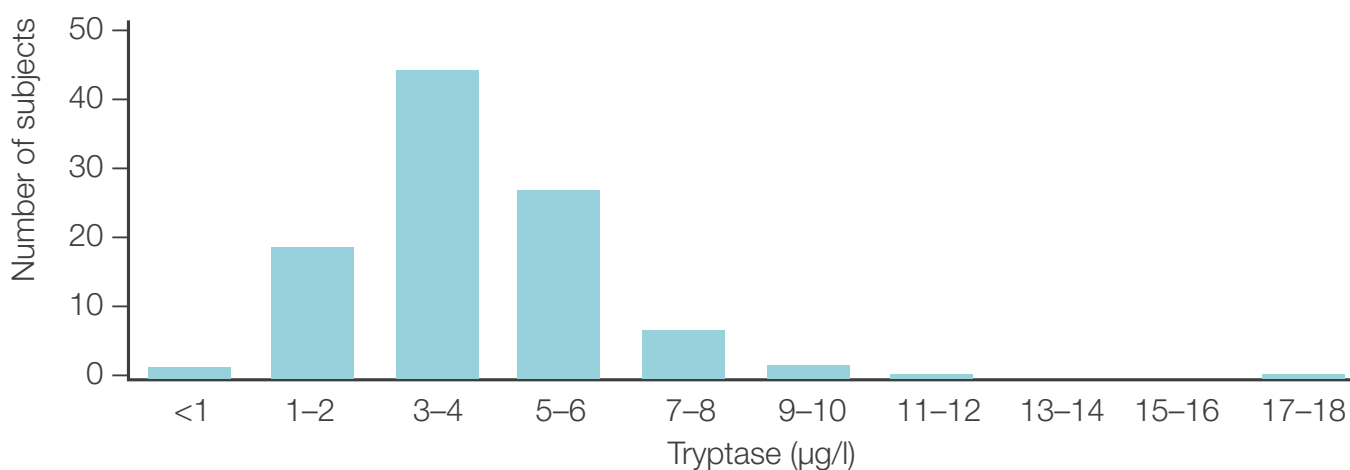
Example: A worried patient seeks help for skin and gastrointestinal problems at a dermatology clinic

## Normal tryptase levels help to rule out systemic mastocytosis

If clinical history and physical examinations made by the dermatology specialist are not consistent with mastocytosis but clearly point at another diagnosis,

a tryptase test within the normal range may support a negative mastocytosis diagnosis.<sup>1</sup> An objective test result also may help reassure the patient.

The baseline tryptase among healthy individuals varies but, in each individual, it is normally stable over time.<sup>12,13</sup>



Distribution of tryptase concentration in a population of 124 healthy individuals as measured with ImmunoCAP Tryptase test:<sup>14</sup>

- Geometric mean: 3.4 µg/l
- 95 upper percentile: 11.0 µg/l

# A proposed test algorithm – as a guide in tryptase evaluation

## Who

- Patients with a suspicion of mastocytosis.
- Patients who have had an anaphylaxis.
- Patients being considered for venom-specific immunotherapy after previous reactions to bee and/or wasp stings.

## Why

- Tryptase is one minor diagnostic criterion of SM.<sup>1</sup>
- Tryptase testing is an aid to confirm mast cell activation in anaphylaxis.
- Tryptase measurement should be considered, together with a thorough case history and relevant specific IgE antibody testing, to help identify the underlying cause of the reaction. Importantly, this can help avoid a potentially life-threatening exposure to the offending substance.

## How

- The baseline level of tryptase in the circulation reflects the number of mast cells. A persistently elevated baseline level of tryptase above 20 µg/l is an indication of possible mast cell disorders and is recognized by the WHO as one minor diagnostic criterion of SM.

# What is tryptase?

Tryptase is an enzyme and is the most abundant granule protein in mast cells. Within the mast cell, mature tryptase is stored in granules as a heparin-stabilized active tetramer.<sup>15,16</sup>

Proforms of α-tryptase and β-tryptase are continuously released into the circulation and constitute the individual baseline tryptase level in serum or plasma. Each individual has his/her own unique baseline level of total tryptase, which is normally stable over time.<sup>12,13</sup>

## Tryptase as a marker for mast cell activation

Human mast cells play a central role in inflammatory processes and in severe reactions, such as anaphylaxis. When mast cells are activated, e.g., during IgE-mediated allergic reactions, they release substances, such as histamine and tryptase, into the local surrounding tissues and the blood. Histamine is a well-known mediator causing allergic symptoms.<sup>2</sup>

While the rapid degradation of histamine makes it impractical as a marker for mast cell activation, tryptase remains stable and functional for several hours. This robustness of tryptase makes it a useful tool for confirming mast cell involvement in severe reactions like anaphylaxis. As the serum baseline tryptase level is stable over time, comparisons can easily be made between peak and baseline values.<sup>2,3</sup>

## Post mortem

An elevated tryptase level has been described in patients in whom death appeared to be due to anaphylaxis. To determine if this is the case, tryptase should be measured close to the time of death, and possibly at certain intervals thereafter.<sup>17</sup>

# ImmunoCAP Tryptase test

The ImmunoCAP Tryptase test measures the total level of tryptase released by mast cells into the circulation. This enables the measurement of transient increases in the level of tryptase after an anaphylactic reaction, as well as establishment of the person's baseline tryptase level. The ImmunoCAP Tryptase test measures all forms of tryptase.

## Collecting a sample

The measuring range is 1–200 µg/l and the amount of serum or plasma needed per test is 40 µl. Both serum and plasma samples from venous blood can be used. There is no need for special procedures when collecting blood or preparing the samples.

## Timing

### To confirm mast cell activation:

Blood samples should be collected as close to the reaction as possible, between 15 minutes and 3 hours after the onset of anaphylactic symptoms. Elevated tryptase levels usually can be detected up to 6 hours following an anaphylactic reaction, and return to baseline levels approximately 24–48 hours after complete resolution of all clinical symptoms.<sup>2,18</sup>

### To measure baseline level:

Blood samples can be collected any time (before or after) outside the period of an acute reaction as described above.<sup>3</sup>

*Limitations of procedure – please refer to limitations contained in Directions for Use.*



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