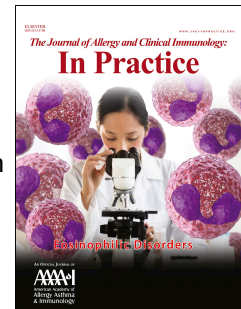


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Usefulness of Testing for Hereditary Alpha Trypsinemia in Symptomatic Patients with Elevated Tryptase

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Clinical Implications

Symptomatic patients with mildly elevated basal serum tryptase may have hereditary alpha tryptasemia, or less commonly, systemic mastocytosis. The results of non-invasive tryptase genotyping may help determine the need for subsequent bone marrow biopsy

To the Editor:

Alpha- and beta-tryptases are mast cell-derived serine proteases encoded by the genes *TPSB2* and *TPSAB1*.^{1,2} Basal serum tryptase (BST) is elevated in 4-6% of Western populations.³ Rarely this is caused by systemic mastocytosis (SM), and more commonly, by hereditary alpha tryptasemia (HαT) an autosomal dominant trait resulting from increased *TPSAB1* copy number encoding alpha-tryptase. SM and HαT are often associated with overlapping symptoms.^{4,5} and distinguishing them on clinical grounds can be challenging. Furthermore, prior to the discovery of HαT, symptomatic patients with borderline elevated tryptase levels created a diagnostic conundrum—could the presentation represent systemic mastocytosis, in which case an invasive bone marrow or tissue biopsy would be warranted?⁶ HαT can be diagnosed by genetic testing⁴ and as such, screening for HαT in patients with elevated BST may potentially reduce the need for biopsy in borderline cases. Herein, we describe how tryptase genotyping can help risk stratify the patients and identify cases needing bone marrow biopsy.

All patients were assessed at a tertiary care teaching hospital and identified by retrospective chart review approved by the St. Michael's Hospital research ethics board.

Patient 1 was a 22-month old female with recurrent flushing of her face, trunk, legs and upper arms which improved with antihistamines. Her skin was hot to the touch but did not appear to be itchy. She had abdominal pain with loose stools. Numerous foods including chicken, strawberry, and avocado caused marked flushing, bloating, constipation and abdominal pain. Physical examination was unremarkable. Her BST levels ranged from 11.9 - 13.4 mcg/L (reference range 3.8 – 11.4 mcg/L). Gastrointestinal endoscopic mucosal biopsies stained for tryptase, CD117, CD2 and CD25 demonstrated no immunohistochemical evidence of mast cell infiltration or aberrant marker expression. Tryptase genotyping revealed an extra allelic alpha-tryptase copy at *TPSAB1*, diagnostic of HαT.

Patient 2 was a 56-year-old woman with a history of frequent syncopal episodes accompanied by itchy skin as a young adult. In her 30s, she had fewer syncopal episodes, but did have recurring presyncope accompanied by bradycardia and episodic facial flushing and swelling. In her 40s, she developed dysautonomia with a positive tilt-table test. She had frequent bloating, nausea, vomiting, abdominal cramping and loose stools. Two *Hymenoptera* sting reactions caused generalised urticaria, wheezing and chest pain; a third caused life-threatening anaphylaxis with asystolic cardiac arrest. ImmunoCAP testing showed elevated specific IgE to honey bee, yellow hornet, yellow jacket, and paper wasp venoms. Alcoholic beverages caused episodes of collapse, whereas opiates caused bradycardia. Strenuous exertion was accompanied by palpitations and flushing, and high ambient temperatures caused presyncope. She had no evidence of joint hypermobility. Her BST ranged from 13.0 - 16.0 mcg/L. She declined to have a bone marrow biopsy (BMBx). Genetic testing also revealed a duplication of *TPSAB1* encoding alpha-tryptase gene.

Patient 3 was a 39-year-old woman who presented with a six year history of recurrent episodes of facial flushing and swelling often accompanied by abdominal cramping and massive diarrhea. Urticaria were seldom present and she had no pruritus or angioedema. She reported light-headedness with postural changes, sometimes culminating in loss-of-consciousness. She had hypermobile joints with a Beighton score of 5-6/9. She had chronic fatigue, night sweats, numbness and tingling in her extremities, decreased energy level and easy bruising. Her tryptase level was 14.3 mcg/L. Catecholamines, metanephrines, VMA and 5-HIAA on 24-hour urine collection were not elevated. Tryptase genotyping did not demonstrated increased *TPSAB1* copy

number. BMBx showed para-trabecular aggregates of spindled mast cells aberrantly expressing CD2 and CD25, and the *KIT* p.D816V variant was identified confirming the diagnosis of SM.

Elevated BST (> 11.4 mcg/L) has been reported in 4-6% of Western populations.³ Myeloproliferative conditions - including mastocytosis and other myeloid neoplasms may be associated with elevated BST,⁷ as can end-stage renal disease.⁸ When BST is elevated independent of these conditions, patients report multiple symptoms including fatigue, arthralgias, myalgias, vertigo, tachycardia, flushing, palpitations, diarrhea and anaphylaxis to drugs, radiocontrast media and insect stings.³ The most common cause for elevated BST in this subset of patients is the autosomal dominant genetic trait H α T which has also been associated with these phenotypes. Other features associated with H α T include irritable bowel syndrome, gastroesophageal reflux disease, and inhalant allergies and asthma.⁴

Symptoms and tryptase levels in H α T and SM may be similar and distinguishing between them can be problematic. Since a BMBx is costly and invasive, patients may be reluctant to undergo this procedure. Alternatively, H α T can be identified via less invasive genetic testing which is generally accepted by patients. Since H α T is considerably more prevalent than SM, screening for H α T may be done before proceeding with a BMBx. However, clonal mast cell disease may occur concomitantly with H α T and positive genetic testing does not rule out myeloid disease.

Herein, we have highlighted three patients ranging in age from 2 to 56 years. All had symptoms of mast cell activation and mildly elevated BST (11.9 – 16.0 mcg/L). Genetic testing revealed H α T in two of the patients and in the case of the youngest patient was reassuring of the decision not to proceed to BMBx. Negative screening in the third patient prompted BMBx to confirm the diagnosis of SM. Given that treatments for H α T and indolent SM both utilize anti-mediator therapy and mast cell stabilizers, there is little potential harm in deferring BMBx until after tryptase genotyping. Indeed, elevated BST in the absence of H α T could raise the pre-test probability of identifying clonal myeloid disease. However, because H α T may occur concurrently with clonal disease,⁹ it does not rule out this diagnosis. Indeed, in patient 2 a bone marrow biopsy was recommended, but was declined. Together, these 3 cases illustrate the complexity of characterizing patients with symptoms of mast cell activation, and the potential utility and limitations of this newly available genotyping assay in clinical practice. Larger studies are required to establish the role of tryptase genotyping when considering BMBx in this context.

References

1. Schwartz LB, Metcalfe DD, Miller JS, Earl H, Sullivan T. Tryptase levels as an indicator of mast-cell activation in systemic anaphylaxis and mastocytosis. *N Engl J Med*. 1987 Jun 25;316(26):1622-6
2. Caughey GH. Tryptase genetics and anaphylaxis. *J Allergy Clin Immunol*. 2006 Jun;117(6):1411-4.
3. Fellinger C, Hemmer W, Wöhrl S, Sesztak-Greinecker G, Jarisch R, Wantke F. Clinical characteristics and risk profile of patients with elevated baseline serum tryptase. *Allergol Immunopathol (Madr)*. 2014 Nov-Dec;42(6):544-52
4. Lyons JJ, Yu X, Hughes JD, Le QT, Jamil A, Bai Y, Ho N, Zhao M, Liu Y, O'Connell MP, Trivedi NN, Nelson C, DiMaggio T, Jones N, Matthews H, Lewis KL, Oler AJ, Carlson RJ, Arkwright PD, Hong C, Agama S, Wilson TM, Tucker S, Zhang Y, McElwee JJ, Pao M, Glover SC, Rothenberg ME, Hohman RJ, Stone KD, Caughey GH, Heller T, Metcalfe DD, Biesecker LG, Schwartz LB, Milner JD. Elevated basal serum tryptase identifies a multisystem disorder associated with increased TPSAB1 copy number. *Nat Genet*. 2016 Dec;48(12):1564-1569.
5. Wilcock A, Bahri R, Bulfone-Paus S, Arkwright PD. Mast cell disorders: From infancy to maturity. *Allergy*. 2019 Jan;74(1):53-63.
6. Valent P, Akin C, Metcalfe DD. Mastocytosis: 2016 updated WHO classification and novel emerging treatment concepts. *Blood*. 2017 Mar 16;129(11):1420-1427.
7. Valent P, Sperr WR, Sotlar K, Reiter A, Akin C, Gotlib J, Horny HP, Arock M. The serum tryptase test: an emerging robust biomarker in clinical hematology. *Expert Rev Hematol*. 2014 Oct;7(5):683-90
8. Jesky MD, Stringer SJ, Fenton A, Ng KP, Yadav P, Ndumbo M, McCann K, Plant T, Dasgupta I, Harding SJ, Drayson MT, Redegeld F, Ferro CJ, Cockwell P. Serum tryptase concentration and progression to end-stage renal disease. *Eur J Clin Invest*. 2016 May;46(5):460-74
9. Sabato V, Chovanec J, Faber M, Milner JD, Ebo D, Lyons JJ. First identification of an Inherited TPSAB1 quintuplication in a patient with clonal mast cell disease. *J Clin Immunol*. 2018 May;38(4):457-459.