UNIVERSITY OF MIAMI
MILLER SCHOOL of MEDICINE

Hereditary Alpha Tryptasemia Syndrome (HαTS): An Autobiographical Case Report and Literature Review of an Under-Recognized Clinical Entity Emulating Irritable Bowel Syndrome (IBS) and Inflammatory Bowel Disease (IBD)

Kavan Maguire Mulloy BS, Third Year Medical Student, Miller School of Medicine, University of Miami, Miami, Florida,
Jamie S. Barkin MD, MACP, MACG, Professor of Medicine, Miller School of Medicine, University of Miami, Miami, Florida

Introduction[1,2]

- HαTS is an autosomal dominant disease first characterized in 2014 by Lyons JJ. et al.[1], and present in ~5% of the Caucasian population.
- It is responsible for ~90% of patients with elevated basal serum tryptase (BST) in western world.
- It modifies clonal and nonclonal mast cell disorders with increased prevalence and/or severity of anaphylaxis and mast cell mediator-related symptoms.
- Variable presentation: 1/3rd of patients are asymptomatic, 1/3rd have mild disease, and 1/3rd have severe disease.
- Emulates functional gastrointestinal disease in 30-50% of patients.
- Flushing and pruritis are present in 30-50% of patients.
- Other symptoms may include food intolerances, IgE-mediated food allergies, dysautonomia, neuropsychiatric manifestations, and joint hypermobility.

Aim and Methods

To present an autobiographical case report and peer literature review of HαTS.

- Review of peer literature selected using search terms: HαTS, Tryptase, IBS, IBD on PubMed.

Case Presentation

Background:

- A 26-year-old male CC of change in bowel habits for 4 years, from 1-2 formed normal stools to passage of up to 6 loose-watery bowel movements (BMs) per day.
- Associated with excessive flatulence, abdominal bloating, crampy abdominal pain relieved by passage of BMs.
- Also associated with generalized pruritus, worse at night, which frequently awakens him from sleep.
- Stomach burning controlled with high dose H2RA.
- Chest and facial flushing with alcohol intake and with exercise.
- Symptom relief on a very low carbohydrate diet. No relief on low-Histamine diet.
- Negative allergy testing with normal celiac & HLA testing, brush border disaccharidases, CBC and CMP, thyroid panel, fecal elastase.
- VIP slightly elevated at 65 pg/mL (nl <58.8 pg/mL).
- EGD and gastric biopsy showed gastritis, negative for H. Pylori.
- Duodenal biopsies showed increased mast cell density at 24 per hpf (nl <15 per hpf) and mildly increased intraepithelial lymphocytes. Colonoscopy yielded normal biopsies.
- Initial serum tryptase was 5.8 ng/mL (nl <8 ng/mL).
- Serum Tryptase repeated two years later was elevated to 12.7 ng/mL mL (nl < 8ng/mL).

Treatment:

- Treated empirically for SIBO with 14-day trial of Rifaximin and for SIFO with a 28-day trial of oral fluconazole with no effects.
- No symptom relief with oral cromolyn.
- Famotidine 20 mg BID and a licorice supplement PRN eliminated gastric burning.
- Pruritus decreased with fexofenadine 720 mg QD, levocetirizine 20 mg QD, and oral ketotifen 2mg QD, Hydroxyzine 25 mg PRN for acute flares.

Diagnosis:

- Genetic PCR testing of buccal swab revealed 1 extra-allelic copy of alpha tryptase gene on TPSAB1 gene locus, consistent with HαTS. Genotype αβ:ααβ.

Literature Review Results

Clinical features of HαTS, IBS, and IBD patients

Clinical Feature	HαTS[2,3]	IBS[4]	IBD
Age of Onset	Unknown	20-30 y/o	major peak 15-25 y/o, minor peak 50-70
Male:Female	Male = Female	Female > Male	Male = Female
Western Prevalence	~5% of Caucasians	10-20%	1.3%
Common Symptoms and Signs	Diarrhea predominant, crampy abdominal, pain, GERD, flushing, and pruritus	Diarrhea and/or constipation, crampy abdominal pain, GERD	Diarrhea, crampy abdominal pain, bloody stools, bowel fistulas, intestinal strictures/fibrosis, weight loss, anemia
Serum Lab Values	Elevated Basal Serum Tryptase (Suspicion Mild-Moderate 6.2-7.9 ng/mL; Suspicion High >8.0 ng/mL)	No significant findings	Elevated C-reactive protein, erythrocyte sedimentation rate, fecal calprotectin, and Iron deficiency
Genetic Characterization	Extra allelic copy of alpha tryptase encoding gene on TPSAB1 gene locus[2]	Normal	+/- Positive
Small Bowel Histology	Increased density of Mast Cells forming 2-15 cell clusters	No significant findings	Granulomas, Inflammation, Ulcerations, and crypt abscesses
Current Treatments	H1 and H2 antihistamines, Ketotifen, Cromolyn*, Omalizumab**	See 2019 ACG Clinical Guidelines	Immunomodulation Therapies

*= No response in symptoms from patient in case study
**= Treatments reported in literature with variable responses and not used by patient in case study

Genetic Characterization:

- HαTS is caused by a common autosomal dominant genetic trait due to increased copy numbers of α-tryptase encoding sequences at the TPSAB1 gene (Figure 1).
- Copy number of both α and β-tryptase sequences are variable with as few as 1 and as many as **8 α** copies reported.
- There exists a gene-dosing effect for α copy number and BST.
- β tryptase copy number variations are well-tolerated.

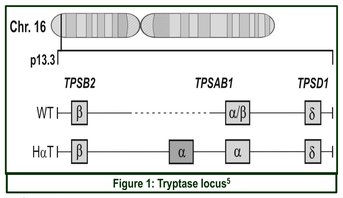

Figure 1: Tryptase locus[5]

Conclusions

- HαTS should be considered, by healthcare providers, in patients with symptoms of IBS and IBD—especially if associated with flushing, pruritis, or dysautonomia.
- Treatments for IBS-D, such as TCAs, will presumably help patients with HαTS given their anti-histaminergic properties alone.
- Treatment regimens are currently aimed to relieve symptoms.
- Omalizumab and other mast cell stabilizing biologics may be effective.
- Increase in basal serum tryptase in HαTS is largely a consequence of increased constitutive secretion of alpha and beta tryptase monomers
- There is an increased concentration of tryptase heterotetramers in HαTS patients at basal tryptase levels.
- The serine protease activity of heterotetramers may play a role in the pathogenesis of symptoms in HαTS and are a current target for novel therapeutic development.
- The overlap of HαTS patients and patients with Mast Cell Activation Syndromes is yet to be fully determined.
- Duodenal biopsies showing increased density of mast cells (>15/hpf) and elevated serum tryptase (>6.5 ng/mL) suggests diagnosis of HαTS.
- Genetic PCR Testing will confirm diagnosis.

Summary

- HαTS is a common disease with symptoms overlapping IBS and IBD

References

1. *Lyons J.J., 2014 ;133(5):1471-1474.*
2. *Wu R., Lyons J.J., 2021;21:33.*
3. *Konnikova L. et al. 2021;148:813-821.e7.*
4. *Lacy B. et al. 2021;116:17-44.*
5. *O'Connell M.P.,Lyons J.J., 2022;* 22:143 – 152
6. Le QT, et al. 2019; 216:2348–2361.

Acknowledgements

A special thank you *to Dr. Wendell Richmond at Rush University Dept. of Allergy and Immunology* for securing my diagnosis in August 2021.