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Case Report

A Case Report of a 12-Year-Old Boy with Hereditary Alpha-Tryptasemia Presenting with Multisystem Symptoms

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Abstract:

Hereditary alpha tryptasemia (HaT) is an autosomal dominant genetic condition characterized by an increased copy number of the TPSAB1 gene encoding alpha tryptase, leading to elevated basal serum tryptase levels. HaT's clinical manifestations vary widely, with some individuals remaining asymptomatic and others experiencing significant symptoms. We report a case of a 12-year-old boy with high-functioning autism and attention deficit hyperactivity disorder (ADHD), presenting with a spectrum of symptoms. The patient exhibited symptoms from the gastrointestinal tract, cardiovascular system, intermittent urticarial rash, angioedema, cough and shortness of breath, lower limb pain, nausea, and difficulty performing daily activities. He was also characterized by intense anxiety and pronounced distractibility. Physical examination and blood tests were unremarkable except for an elevated basal serum tryptase level. Following a thorough investigation, hereditary alpha-tryptasemia was confirmed by genetic screening. Given the broad spectrum of HaT manifestations and its prevalence, HaT should be considered in patients with similar clinical features. Further research is necessary to understand the full clinical implications of HaT and to develop comprehensive management guidelines.

Keywords: Hereditary Alpha-tryptasemia, multisystem, mast cell, children.

Introduction

In 2014, it was first reported that elevated basal serum tryptase levels could be inherited through an autosomal dominant pattern, leading to the formal recognition of hereditary alpha-tryptasemia (HaT) (1, 2). Hereditary alpha-tryptasemia is a newly identified autosomal dominant genetic trait characterized by an increased copy number of the TPSAB1 gene encoding alpha a-tryptase. This condition typically results in elevated basal serum tryptase levels and is linked to various clinical manifestations (3).

Both basal serum tryptase levels and severity of clinical symptoms display a gene dose relationship with TPSAB1, whereby higher tryptase levels and greater symptom severity are correlated with increasing numbers of alpha-encoding TPSAB1 copies. Elevated basal serum tryptase (BST), typically reported as more significant than 11.4 ng/mL, is characteristic of individuals with HaT. When excluding HaT cases, population-based evaluations show a median BST level of approximately 4 ng/mL, with the upper limit nearing the clinical

laboratory threshold of 11.4 ng/mL (4).

HaT is estimated to affect approximately 5.7% of the general population in the Western world. While some individuals may exhibit minimal or no symptoms, others experience a wide range of impairing symptoms (4). Dermatological manifestations include flushing, pruritus, angioedema, and occasionally, urticaria. Gastrointestinal disturbances are reported, such as bloating, pain, and diarrhea. Connective tissue irregularities include joint hypermobility, deformities, pain, and primary tooth retention. Furthermore, symptoms indicative of autonomic dysfunction were identified, with some individuals presenting with postural orthostatic tachycardia syndrome (POTS). Behavioral complaints and sleep disturbance are not unusual in these patients. The HaT is linked to increased frequency and severity of immediate hypersensitivity reactions, especially in individuals suffering from Hymenoptera venom allergy (4-7).

In pediatric patients, the clinical presentation of hereditary alpha-tryptasemia is notably underdefined, rendering differential diagnosis particularly complex. Disorders such as systemic mastocytosis, pheochromocytoma, and mast cell activation syndrome exhibit overlapping pathophysiology and symptoms, further complicating the distinction among these conditions (8). This case report describes a pediatric patient with HaT, who presented with multisystem symptoms.

Case Report

We present the case of an obese 12-year-old boy diagnosed with high-functioning autism and attention deficit hyperactivity disorder (ADHD) who exhibited a four-month history of abdominal pain, alternating constipation, diarrhea, frontal headache with dizziness, intermittent urticarial rash, angioedema, occasional cough and shortness of breath, lower limb pain with intermittent ankle joint swelling and lameness, nausea, and difficulty performing daily activities. Notably, these symptoms have progressively deteriorated over the past two weeks. Symptoms were triggered after exercise and partially responded to cetirizine but recurred after therapy discontinuation. It is also noteworthy that he exhibited further behavioral disorganization, characterized by intense anxiety and pronounced distractibility. An antipsychotic drug was prescribed but was only administered a few times.

With regard to the previous history, the patient was born preterm at 34 weeks gestation and was hospitalized for ten days due to respiratory distress syndrome. He presented an urticarial rash in the past following the administration of Cefaclor and Ibuprofen. Mother has Hashimoto’s disease and Polyostotic Fibrous Dysplasia

associated with McCune-Albright syndrome and has experienced headaches, dizzy spells, and vertigo from a young age. Additionally, the patient's maternal grandmother has a history of chronic urticaria, dermographism, and chronic depressive disorder and was recently diagnosed with colon cancer.

During the physical examination, no pathological findings were observed in the child. He underwent a comprehensive diagnostic work-up, including complete blood count, liver and kidney function tests, celiac disease screening, stool culture, total immunoglobulin (Ig) and IgE levels, thyroid function tests, skin prick tests for inhalant allergens, and RAST for food allergens, which were normal apart from an elevated basal serum tryptase level of 20 ng/mL. The abdominal ultrasound was unremarkable. A bone marrow biopsy was performed to rule out systemic mastocytosis, which showed no morphologic, immunophenotyping, or cytogenetic abnormalities, and the c-KIT D816V mutation analysis on the bone marrow specimen was negative. Subsequently, a genetic test using digital PCR (dPCR) was performed to diagnose HaT. The results indicated an additional allelic copy of TPSAB1, consistent with HaT, resulting in the pathological genotype 3a:2b.

The child was treated with bilastine, which presented a significant remission of his symptoms. Genetic testing was recommended to the child’s family.

Discussion

Hereditary alpha tryptasemia (HaT) is a relatively new diagnosis in the realm of genetic disorders, formally recognized only in recent years. This autosomal dominant condition, characterized by an increased copy number of the TPSAB1 gene encoding alpha tryptase, leads to elevated basal serum tryptase levels, which can present a broad spectrum of clinical manifestations. We present the case of the 12-year-old boy described in this report, which underscores the complexity and variability of HaT symptoms, emphasizing the need for heightened awareness among clinicians.

This patient exhibited a wide array of symptoms, ranging from gastrointestinal and dermatological issues to musculoskeletal pain and behavioral disturbances, which progressively worsened over a four-month period. The most prominent and life-limiting symptoms in this patient were abdominal pain, constipation, headache, fatigue, and urticarial rash, which have also been reported in other studies. In a study from the U.K., which investigated the prevalence of HaT, allergic symptoms were the most common among patients, followed by the gastrointestinal tract (9). In the U.S., patients with HaT are 2-5 times more likely to suffer from functional

gastrointestinal symptoms compared to the population average (10).

The elevated basal serum tryptase level of 20 ng/mL was a crucial diagnostic clue that prompted further genetic testing, ultimately confirming the diagnosis of HaT with a 3a:2b genotype. This highlights the importance of considering HaT in patients with multisystem symptoms, particularly when common diagnostic evaluations fail to reveal clear pathologies. Nevertheless, there is a debate in the literature regarding the level of BST to commence investigations for HaT (11). Most studies show that most individuals with HaT have BST ranging from 8-11.3 ng/ml. In contrast, in normal individuals, BST has been found to fluctuate between 1.0-11.4ng/ml; hence, recently, it has been proposed that all individuals with BST higher than 8 ng/ml be investigated for HaT (12).

The overlap in clinical features between HaT, systemic mastocytosis, and mast cell activation syndrome complicates the differential diagnosis. In this case, excluding systemic mastocytosis through bone marrow biopsy and c-KIT D816V mutation analysis was essential in narrowing down the diagnosis. The use of digital PCR to detect an additional TPSAB1 copy number was pivotal in confirming HaT, demonstrating the utility of advanced genetic testing in diagnosing hereditary tryptase disorders. Other conditions that may manifest with raised BST and need to be excluded are chronic renal failure, eosinophilic neoplasms and chronic eosinophilic leukemia, myeloid and myelomastic leukemia, obesity, and chronic inflammation and infection, such as filariasis (13).

Although genetic testing has not yet been conducted in the boy's family, maternal inheritance appears likely. The mother and maternal grandmother have exhibited atypical symptoms that significantly impacted their daily lives, like headache, dizziness, chronic urticaria, and depression. Hence, apart from the patient's clinical history and levels of BST, if there is also a positive family history of similar symptoms that cannot be explained, then high suspicion of HaT needs to be exerted.

The management of this patient with Bilastine, an H1 receptor antagonist, significantly improved symptoms. Currently, limited data exists to support a standardized approach for managing HaT, with treatment strategies primarily aimed at symptom management. For cutaneous and gastrointestinal symptoms, high-dose H1 and H2 antihistamines taken twice daily have been recommended, with some patients finding relief through oral ketotifen. Oral cromolyn has also been employed for gastrointestinal symptoms in patients with severe symptoms and elevated mast cell counts in their biopsies. A few patients who have received omalizumab for

allergic asthma reported improvement in some additional symptoms (5, 6).

Informal evidence indicates that medications such as tricyclic antidepressants, clemastine fumarate, and gabapentin may provide some symptomatic relief. For individuals experiencing recurrent severe systemic symptoms or anaphylaxis, it is imperative to identify and avoid triggers, with the provision of epi-pens as the standard of care. There is a pressing need for more effective treatments to alleviate the symptoms associated with HaT. Moreover, the lack of prospective clinical trials considerably hampers evaluating current treatment efficacy in these challenging cases (5, 6).

Given the estimated prevalence of HAT in approximately 5.7% of the general population, many cases are likely to remain undiagnosed. Clinicians should maintain a high index of suspicion for HAT in patients with unexplained multisystem symptoms and elevated serum tryptase levels (≥8 ng/ml). Based on similar family history, we recommend obtaining a baseline tryptase level in patients with refractory functional gastrointestinal disease and allergic cutaneous symptoms, especially when associated with joint hypermobility, headache, and chronic fatigue.

This case report contributes to the growing knowledge of HaT, providing insights into its clinical presentation, diagnostic challenges, and management strategies. Continued documentation and study of such cases will improve our understanding and care of patients with hereditary alpha tryptasemia.

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