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REVIEW

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Hereditary Alpha Tryptasemia

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ABSTRACT

Hereditary alpha tryptasemia (HAT) is currently considered a fully penetrant genetic trait. An increased germline copy number of the TPSAB1 gene results in HAT. Hereditary alpha tryptasemia is estimated to affect 4%-6% of the Western population. The association between HAT and mast cell disorders is well established. Several studies have demonstrated a correlation between idiopathic anaphylaxis and HAT, with HAT detected in approximately 17% of patients presenting with idiopathic anaphylaxis. Patients exhibiting symptoms of mast cell activation, including anaphylaxis and gastrointestinal manifestations, and with basal serum tryptase (BST) levels exceeding 8 ng/mL should be considered for tryptase genotyping by digital droplet polymerase chain reaction. Currently there are no treatment modalities specific to HAT. Treatment focuses on alleviating symptoms and is intended for long-term management.

Keywords: Hereditary alpha tryptasemia, anaphylaxis, tryptase, mastocytosis

INTRODUCTION

Hereditary alpha tryptasemia (HAT) is an autosomal dominant genetic condition first described by Lyons et al. in 2016. It is characterized by the presence of one or more extra copies of the α-tryptase allele at the TPSAB1 locus (1, 2). An increased copy number of TPSAB1, which encodes α-tryptase, results in elevated basal serum tryptase (BST) levels (3). In all individuals with HAT, BST levels above 8 ng/mL have been observed (1). Studies have demonstrated a positive correlation between the severity of symptoms in HAT patients and the number of TPSAB1 gene copies, indicating a gene-dose effect (4). Persistently elevated BST levels are a significant indicator for screening systemic clonal mast cell diseases, particularly systemic mastocytosis (SM) (5). Given that HAT is a recently described condition with potential implications for allergy practice, this review aims to provide an up-to-date overview of its diagnosis and management.

1. Mast cells and tryptase

Tryptase is predominantly expressed by mast cells and, to a lesser extent, by basophils (6, 7). Mature tryptases, composed of 245 amino acids, form tetramers that are stored in mast cell granules and are derived from processed pre-tryptase, a 274-amino acid precursor peptide (Figure 1) (8). Enzymatically active tetramers are stabilized by heparin at low pH within granules and are released during mast cell activation (9). Mature tryptases are involved in various processes, including DNA modification, tissue repair, vascular permeability, neutrophil and eosinophil chemotaxis, and thrombolysis (Figure 2) (8).

The majority of measured BST in healthy individuals comes from protryptases, which are secreted into the serum in their monomeric form and have not yet been converted into mature tetrameric tryptases (1). Hereditary alpha tryptasemia is characterized by elevated levels of pro-α-tryptase in the bloodstream, resulting from extra copies of the TPSAB1 gene (which encodes α-tryptase) and associated overactive promoter elements. Elevated relative levels of α-tryptase have been associated with an increased formation of α/β-tryptase heterotetramers (9).

A BST level exceeding 11.4 ng/mL, considered elevated, appears to be relatively common in the general population, with an estimated prevalence of 4% to 6%. Elevated

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BST levels may also be observed in individuals with end-stage renal disease, mast cell disorders, and older adults (1, 5). Obesity and smoking are associated with elevated BST levels in the general population, whereas alcohol consumption has been linked to lower levels (8). A correlation between increased tryptase values and both older age and a body mass index exceeding 25 kg/m² has been reported (10). Mature tryptases are tetrameric structures composed of either α-tryptase or β-tryptase subunits, and they can also exist as heterotetramers containing both. These serine proteases are important mediators of anaphylaxis (9, 11). Mature α-tryptase homotetramers are catalytically inactive, whereas mature β-tryptase homotetramers demonstrate enzymatic functionality (7). α/β-heterotetramers exert their effects by activating epidermal growth factor (EGF)-like module-containing mucin-like hormone receptor 2-like (EMR2) and protease-activated receptor 2 (PAR2). In vitro, these heterotetramers may lower the threshold for mast cell degranulation induced by vibration (4). Activation of EMR2 by vibration results in flushing, urticaria, pruritus and angioedema. PAR2 activation is associated with increased vascular endothelial permeability and smooth muscle contraction (12).

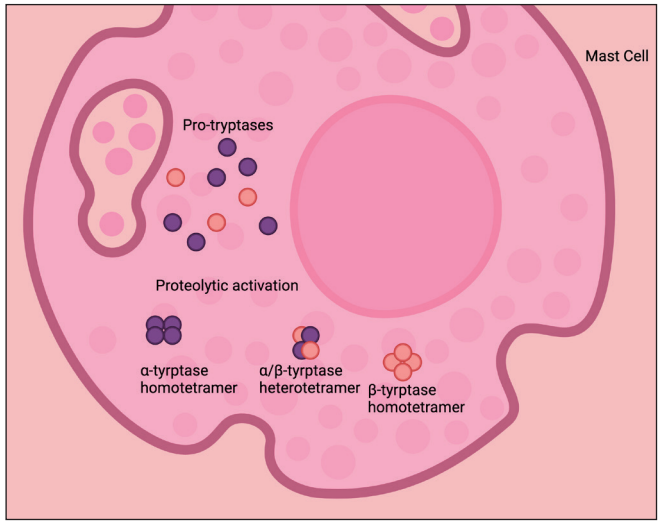


Figure 1. Tryptase production in mast cells.

2. Prevalence and risk factors

Hereditary alpha tryptasemia is estimated to affect 4%-6% of the Western population (8). Similarly, the prevalence of HAT was reported to be 5% of the people in the United Kingdom and 7.5% in the USA (13, 14). The prevalence of HAT in Spain among 346 healthy donors within a larger study of 959 subjects was found to be 4% (15). Its prevalence in France was reported to be 6% (16). The prevalence of HAT in the general Turkish population is currently unknown. HAT prevalence is particularly high among individuals with elevated BST levels or those at the upper limit of normal, affecting approximately 64-72% of cases, and is more common in individuals with systemic mastocytosis (16). Patients with mastocytosis who have BST levels of 8 ng/mL or higher are required to undergo molecular genetic testing for HAT (16).

HAT predominantly affects individuals of white ethnicity (7). Individuals with symptomatic HAT are more frequently female (17). While not yet supported by evidence, it may be speculated that hormones have a potential impact similar to their role in asthma and other atopic

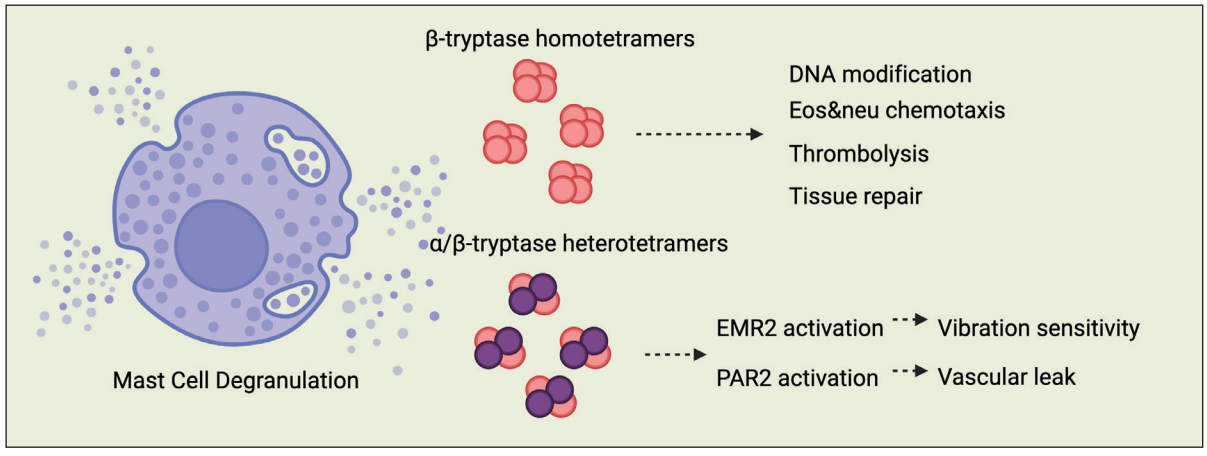


Figure 2. The effects of mature tryptases

**EMR: Epidermal growth factor-like module-containing mucin-like hormone receptor-like 2. *PAR2: Protease-activated receptor 2*

diseases (5, 17-19). A study from the USA suggested that the predominance of females in the patient population may be attributable to increased symptom penetrance in females and lower symptom reporting rates among males (19). Based on the predominance of women over 50 years of age observed in several studies, it has been hypothesized that the menopause may play a contributory role (5, 19, 20). According to another study, this may be explained by selection bias (5). Currently, the existing evidence remains insufficient to support definitive conclusions.

HAT is at present considered a fully penetrant genetic trait (1). An increased germline copy number of the TPSAB1 gene results in HAT (5). The locus for tryptase is situated at position p13.3 on the distal end of the short arm of chromosome 16 and contains four genes that encode for tryptases: TPSG1, TPSB2, TPSAB1, and TPSD1. Although all of these genes encode tryptases, the secreted forms measured and reported as serum tryptase by clinical laboratories are produced only by TPSAB1 and TPSB2 (1). Unlike TPSB2, which encodes only beta-tryptase, TPSAB1 encodes both α- and β-tryptase isoforms (5).

3. Clinical presentation

The first studies to define patients with HAT were conducted at highly specialized medical centers that specifically recruited individuals with concomitant conditions such as connective tissue disorders or autonomic dysfunction. These studies described syndromic clinical features, including congenital hypermobility and postural orthostatic tachycardia syndrome (POTS); however, these findings were not supported by subsequent studies (15, 21). Even after correction for multiple comparisons, HAT was found to be significantly associated with both dysphagia and retained primary dentition (7).

Patients may be asymptomatic or may present with a wide range of symptoms (11, 16). Symptoms are often triggered by infections, medication use, or emotional stress (16). Although HAT is present from birth, no cases of de novo increase in TPSAB1 have been reported, and many individuals become symptomatic later in life, particularly after puberty (17). Clinical manifestations of HAT were described in the initial publications, including systemic immediate hypersensitivity reactions, pruritus and flushing, gastrointestinal symptoms, connective tissue disorders, and autonomic dysfunction. Specific dermatological and gastrointestinal findings have been shown to be significantly associated with HAT in both well- characterized and unselected populations (Table I) (17).

The most prevalent clinical symptoms reported by individuals with HAT are functional gastrointestinal disorders. Based on the Rome III criteria, approximately half of the affected individuals in highly symptomatic families and one-third of those unselected populations have been diagnosed with irritable bowel syndrome (1). However, a more recent cohort study found no association between irritable bowel syndrome and HAT (17).

Approximately half of the symptomatic individuals experience recurrent cutaneous symptoms such as flushing and pruritus. These symptoms often occur spontaneously but may also be triggered by minor stimuli, including vibration or hand clapping (12). Angioedema and urticaria are uncommon manifestations (1). Additional common clinical features of HAT include neuropsychiatric symptoms such as depression, sleep disturbances, memory impairments and fatigue (12, 16). Elevated BST levels are associated with increased risk of severe anaphylaxis (22). Several studies have demonstrated an association between idiopathic anaphylaxis and HAT (15, 21). Hereditary alpha tryptasemia has been identified in 17% of patients with idiopathic anaphylaxis (12). Additionally the prevalence of idiopathic anaphylaxis among patients with HAT is 14% (16).

Table I. Clinical characteristics of patients with hereditary alpha tryptasemia

Cutaneous symptoms: Pruritus/flushing, urticaria, angioedema
GIS symptoms: Abdominal pain, diarrhea, irritable bowel syndrome, dysphagia, odynophagia, dyspepsia,
Musculoskeletal problems: Joint hypermobility, retained primary dentition, arthralgia
C**ardiac symptoms**: Palpitation, orthostatic hypotension, tachycardia, syncope
Neuropsychiatric symptoms: Concentration difficulties, body pain, headache, depression, sleep disorders, memory problems
Systemic symptoms: Systemic venom reaction, idiopathic anaphylaxis

4a. Hereditary alpha tryptasemia and Hymenoptera venom allergy (HVA)

Individuals with venom allergy are more likely to experience severe anaphylaxis if they also have HAT (7). There was no significant difference in HAT prevalence between HVA patients and the general population (7, 16). Findings from a Slovenian cohort were consistent with these data. In contrast, a cohort study from Italy revealed that HAT was at least twice as common in individuals with severe hymenoptera-venom induced anaphylaxis (4) HAT does not trigger the development of hymenoptera venom allergy sensitization; however, it modifies the clinical outcomes. The unique activities of α/β-tryptase heterotetramers, and particularly their effects on vascular permeability and anaphylaxis severity, are key factors in this modification (17). Individuals with venom allergy should undergo BST measurement; if BST levels are ≥8 ng/mL, tryptase genotyping and cKIT D816V mutation testing should be performed (16).

4b. Hereditary alpha tryptasemia and mast cell diseases

Systemic mastocytosis arises from a clonal, neoplastic expansion of mast cells that are morphologically and immunophenotypically abnormal, leading to their accumulation in one or more organ systems (23). The diagnostic criteria for mastocytosis, revised by the WHO, are presented in Table II (adapted from Valent et al.) (24).

Cohort studies from the European Union and the United States have revealed that clonal mast cell diseases and HAT are frequently associated (7). The prevalence of HAT has been reported as 4%, 29%, and 18% respectively in the general population, in individuals with non-clonal mast cell activation syndrome (MCAS), and in patients with mastocytosis (15). Another study reported that the prevalence of HAT in mastocytosis ranges from 9% to 20% (25). Compared to the general population, individuals with SM are approximately 2 to 3 times more likely to have HAT (8).

The coexistence of systemic mastocytosis and HAT is associated with higher BST levels, an increased ratio of hymenoptera venom allergy, and severe symptoms related to cardiovascular mediators (15). Mastocytosis patients with HAT are more prone to anaphylaxis (15). The prevalence of idiopathic anaphylaxis in mastocytosis was reported to be 39% (26). The prevalence of systemic anaphylaxis is approximately twice as high in individuals with both systemic mastocytosis and HAT compared to those with systemic mastocytosis alone (27).

DIAGNOSIS

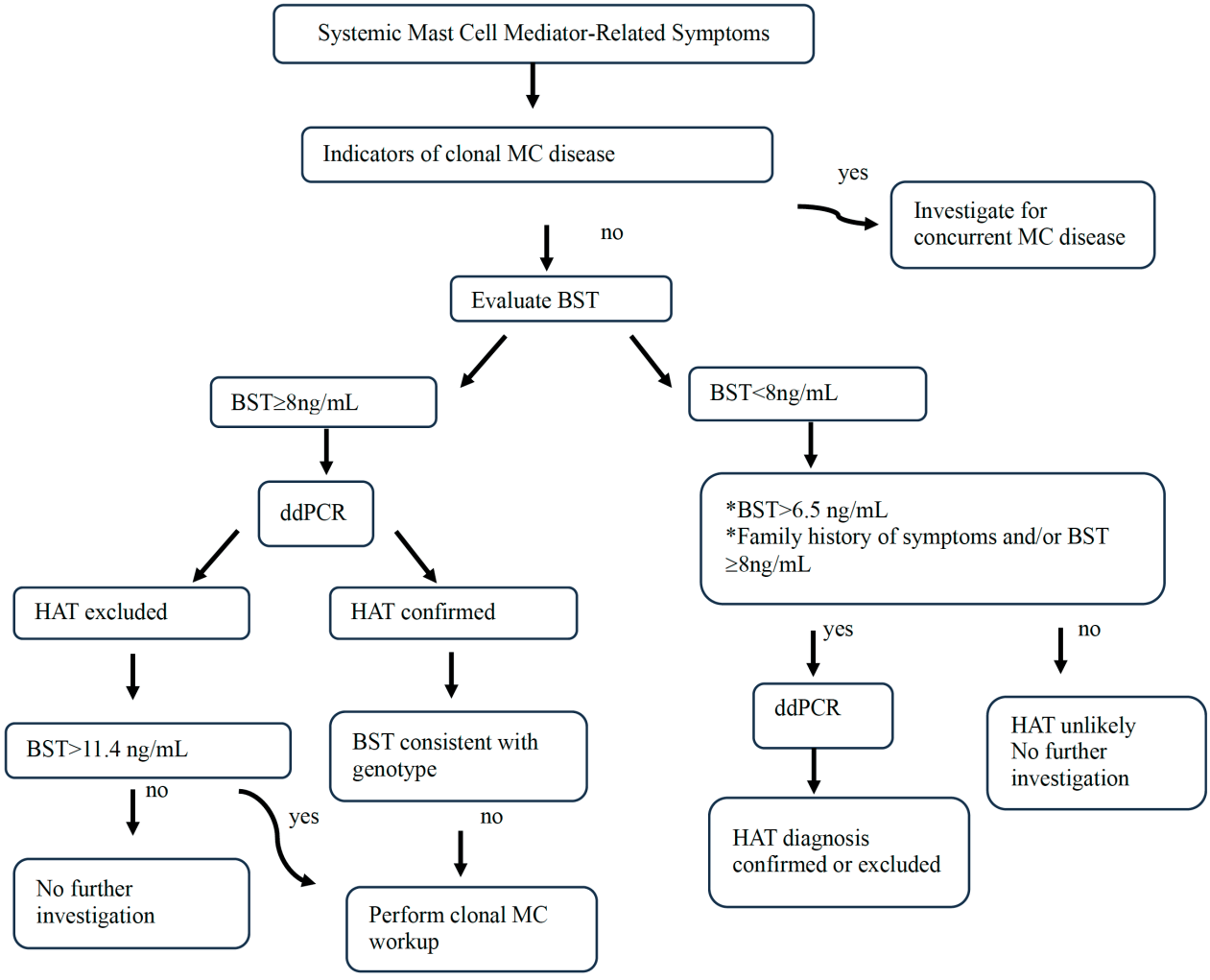
The primary step in diagnosing HAT is to obtain a detailed medical history and assess the need for genetic testing. Patients who exhibit symptoms of mast cell activation, experience anaphylaxis and gastrointestinal complaints, and have a BST exceeding 8 ng/mL should undergo tryptase genotyping via digital droplet polymerase chain reaction (ddPCR). The ddPCR assay demonstrates high sensitivity (100%) and specificity (90%) for identifying HAT in individuals with elevated BST levels (8). Tryptase genotyping may be considered in patients with BST levels >6 ng/mL, particularly if there is a family history of elevated BST levels >8 ng/mL (17). The diagnostic algorithm is presented in Table III (8).

Table II. WHO Revised Systemic Mastosytosis Criteria (adapted from Valent et al.)(24)

Major Criterion
*Multifocal dense infiltrates of mast cells (≥ 15 mast cells in aggregates) in bone barrow biopsies and/or in sections of other extracutaneous organs
Minor Criteria
*≥ 25% of all mast cells are atypical cells on bone marrow smears or are spindle-shaped in mast cell infiltrates detected in the bone marrow or other extracutaneous organs
*KIT-activating point mutation(s) at codon 816 or in other critical regions of KIT in the bone marrow or another extracutaneous organs
*Mast cells in the bone marrow, blood, or another extracutaneous organ express one or more of CD2 and/or CD25 and/or CD30
*Baseline serum tryptase concentration >20 ng/mL (in case of an unrelated myeloid neoplasm, an elevated tryptase does not count as a systemic mastocytosis criterion. In case of known HAT, tryptase levels should be adjusted)

*1 major and 1 minor criterion or 3 minor criteria

Table III. Diagnostic algorithm of hereditary alpha tryptasemia



Tryptase genotyping is recommended for individuals with HVA and BST levels above 8 ng/mL, as well as for those with a history of severe venom-induced anaphylaxis or those considered at risk, even if their BST levels fall within the normal range of 6-8 ng/mL. To date, no individual with HAT and BST levels below 6 ng/mL has been reported or observed, including among patients with HVA (17).

MANAGEMENT

Hereditary alpha tryptasemia treatment focuses on alleviating symptoms and is intended for the long term (16). There are no currently available HAT-specific treatment modalities. Antihistamines, leukotriene antagonists, mast cell stabilizers, aspirin, and corticosteroids are commonly used therapeutic agents. (4). Non-sedating H1 and H2 antihistamines, particularly the latter for gastrointestinal issues, have shown their effectiveness in treatment. In cases of functional tachycardia, H2 receptor antagonists or beta blockers may be appropriate treatments (16). In individuals whose gastrointestinal symptoms are severe, cromolyn sodium may also be administered orally. Oral ketotifen may also improve symptoms (1).

Omalizumab is a monoclonal antibody that downregulates FceRI expression on mast cells and basophils by binding to circulating IgE (28). The benefit of omalizumab in HAT is considered to be primarily related to IgE-mediated pathways, through the reduction of free IgE levels and FcεRI expression on both mast cells and basophils. Robust evidence remains limited to entirely exclude non-IgE-mediated pathways (29, 30). It has been reported to alleviate symptoms such as flushing, urticaria, fatigue, and pain in a limited number of patients (29). It is widely recognized for its effectiveness in relieving symptoms of urticaria and anaphylaxis (19). Desensitization is critical for individuals with HAT and insect venom allergies due to the increased risk of severe anaphylaxis. Lifelong desensitization is recommended for individuals with high-grade anaphylaxis, mastocytosis, or elevated BST levels (16).

Individuals who experience anaphylaxis and/or recurrent severe systemic events should identify and avoid potential triggers. Adrenaline autoinjectors should also be prescribed. In some cases, tricyclic antidepressants and gabapentin have been reported to provide symptomatic relief (1). Although evidence remains limited and no clinical trials support their use, these agents may be considered in symptomatic, carefully selected patients based on anecdotal reports.

Evaluation for bone loss is recommended in individuals with HAT for several reasons. These include bone marrow infiltration by mast cells, cumulative exposure to frequently administered systemic corticosteroids, and the observed association between osteopenia or osteoporosis and elevated BST levels (17).

Noncompetitive inhibitory antibodies that bind to both α- and β-tryptases were developed by Maun et al., and induce the dissociation of active tetramers into monomers in *in vitro* settings (31). Since α/β heterotetrameric tryptases are implicated in various reported clinical symptoms, targeting tryptase may offer therapeutic potential in mast cell-associated disorders. However, currently available data are limited (4, 32, 33). While a phase 2 randomized controlled trial indicated that anti-tryptase antibodies were ineffective in adequately inhibiting tryptase levels in bronchial fluid, their therapeutic potential has not yet been assessed in individuals with HAT (34). These agents have not yet received approval for clinical use in the management of HAT. Prospective clinical trials are needed for the management of difficult-to-treat patients (1).

CONCLUSION

Hereditary alpha tryptasemia is an autosomal dominant genetic trait caused by an increased copy number of the TPSAB1 gene. Mast cell-related symptoms and elevated BST levels are significant indicators for the diagnosis. In suspected cases, ddPCR is performed to confirm the diagnosis. Recently published data have suggested a symptom-based approach for managing symptomatic individuals with HAT; however, there is currently no specific treatment for HAT.

FUTURE OUTLOOK

Neutralizing antibodies to tryptase may represent promising future therapeutic alternatives (31, 32). A multitude of therapeutic agents with potential clinical utility for symptomatic patients with HAT is presently under investigation in ongoing clinical trials. Among the emerging therapeutic strategies currently under investigation are monoclonal antibodies targeting interleukin-33 and sialic acid-binding immunoglobulin-like lectin 8 (SIGLEC-8) (17, 35-37). It is considered that SIGLEC-8 is a possible candidate for further research in the management of HAT (4). An additional group of therapeutic agents with potential future utility includes kinase inhibitors-such as BTK inhibitors-which have recently been shown to reduce mast cell reactivity in humans (38). To date, there are no published clinical data supporting the use of any of these agents. In the future, as our understanding of the pathophysiological mechanisms underlying HAT expands, new therapeutic targets are expected to emerge for the management of symptomatic patients.

Conflict of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Authorship Contributions

Concept: **Ece Sahinoglu, Sevim Bavbek,** Design: **Ece Sahinoglu, Sevim Bavbek,** Data collection or processing: **Ece Sahinoglu, Sevim Bavbek,** Analysis or Interpretation: **Ece Sahinoglu, Sevim Bavbek,** Literature search: **Ece Sahinoglu, Sevim Bavbek,** Writing: **Ece Sahinoglu, Sevim Bavbek,** Approval: **Sevim Bavbek.**

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