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THE ROLE OF TRYPTASE IN THE HUMAN BODY: FROM NORMAL TO PATHOLOGY

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УЛОГА ТРИПТАЗЕ У ЉУДСКОМ ТЕЛУ: ОД НОРМАЛНОГ ДО ПАТОЛОШКОГ СТАЊА

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ABSTRACT

Objective. The study's objective was to examine the impact of the tryptase enzyme on human physiological function in normal and diseased settings.

Methods. Tryptase plays a role in regulating the growth and development of mesenchymal cells, fibroblasts, and endothelial cells, as well as in blood coagulation, metabolic activities of connective tissue, and the contractility of smooth muscle cells. Under pathological conditions, impaired tryptase metabolism leads to excessive fibrosis, development of keloid scars, narrowing of kidney vessels, transplant rejection, development of inflammatory bowel disease, arthritis, psoriasis, atopic and contact dermatitis.

Results. The normal level of serum tryptase is 5 ng/ml. The threshold value of the enzyme is 11.4 ng/ml. Increased levels of this enzyme are found in 4-6% of the population. Increased serum tryptase levels are diagnosed in hereditary pathologies (hereditary alpha-tryptasemia) and acquired diseases (mastocytosis, monoclonal mast cell activation syndrome, anaphylaxis, chronic kidney disease). The clinical picture is characterized by lesions of the cardiovascular, gastrointestinal, respiratory, excretory, and integumentary systems and the development of anaphylaxis.

Conclusion. The pathogenesis of the diseases is still under investigation, so the treatment of the described pathologies is mainly symptomatic. It is concluded that tryptase is the main biomarker of mast cell function, and that impaired metabolism of this enzyme leads to a number of severe, life-threatening pathologies.

Key words: *mast cells; mastocytosis; neoplasms; anaphylaxis; tryptases.*

САЖЕТАК

Циљ. Циљ студије био је да се испита утицај ензима триптазе на физиолошке функције човека у нормалним и патолошким условима.

Методе. Триптаза има улогу у регулацији раста и развоја мезенхимских ћелија, фибробласта и ендотелних ћелија, као и у процесу коагулације крви, метаболичким активностима везивног ткива и контрактилности глатких мишићних ћелија. У патолошким условима, поремећај метаболизма триптазе доводи до прекомерне фиброзе, развоја келоидних ожиљака, сужења бубрежних крвних судова, одбацивања трансплантата, развоја инфламаторних болести црева, артритиса, псоријазе, атопијског и контактног дерматитиса.

Резултати. Нормални ниво триптазе у серуму износи 5 нг/мл, док је праг вредности ензима 11,4 нг/мл. Повишени нивои овог ензима присутни су код 4–6% популације. Повишени нивои серумске триптазе дијагностикују се у наследним патологијама (наследна алфа-триптаземија) и стеченим болестима (мастоцитоза, моноклонски синдром активације мастоцита, анафилаксија, хронична бубрежна болест). Клиничка слика карактерише се оштећењима кардиоваскуларног, гастроинтестиналног, респираторног, екскреторног и интегументарног система, као и развојем анафилаксије.

Закључак. Патогенеза описаних болести и даље је предмет истраживања, те је лечење углавном симптоматско. Закључује се да је триптаза главни биомаркер функције мастоцита и да поремећај метаболизма овог ензима води ка бројним тешким, животно угрожавајућим патолошким стањима.

Кључне речи: *мастоцити; мастоцитоза; неоплазме; анафилаксија; триптазе.*

INTRODUCTION

Increased baseline serum tryptase levels are frequently observed, occurring in 4-6% of the general population. Tryptase is an important marker for assessing mast cell activation. An increase in the level of this enzyme is a predictor of a number of diseases and may also indicate the terminal stages of diseases (chronic kidney disease and systemic mastocytosis) (1). Elevated blood tryptase levels are correlated with an enhanced anaphylactic reaction to hymenopteran bug bites (2). Consequently, these patients exhibit an elevated risk of anaphylactic shock relative to the general population. This results in a decline in quality-of-life heightened anxiety, and limitations on outside activities due to the fear of allergen exposure.

P. Valent et al. (3) show that hereditary alpha-tryptase (HaT), which manifests in an autosomal dominant fashion, is the predominant source of increased basal serum tryptase levels. Research shows that α-tryptase deficiency is more prevalent in Europeans and less common in Asians. At the same time, no cases of b-tryptase deficiency have been described. E.J. Kozyra et al. (4) and J. Shea et

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al. (5) reported rare genetic causes of elevated serum tryptase levels. PLCG2-associated antibody deficiency and immune dysregulation, commonly known as PLAID, is a rare hereditary condition that follows an autosomal dominant inheritance pattern (5). This genetic disorder affects the immune system, causing both antibody deficiencies and dysregulated immune responses in affected individuals. This condition manifests through cold urticaria, frequent bacterial infections, autoimmune complications, and the development of skin granulomas (5). When exposed to cold temperatures, patients experience mast cell degranulation in the skin. In contrast, GATA2 deficiency represents a distinct genetic disorder classified under myelodysplastic syndromes (4). While patients with GATA2 deficiency show elevated blood tryptase levels, they do not exhibit symptoms of mast cell activation (4). These individuals face an increased risk of developing myeloid malignancies, which are associated with higher serum tryptase concentrations.

Elevated levels of tryptase are also found in some acquired pathologies. An elevated enzyme level of 15 ng/ml serves as a biomarker for several conditions including myeloid neoplasms and various mast cell diseases such as mastocytosis, monoclonal and mast cell activation syndrome, and anaphylaxis. Mast cell activation syndromes typically present with systemic recurrent mast cell activation, commonly manifesting as anaphylaxis. These conditions can be influenced by various risk factors including genetic predisposition, existing comorbidities, and hypersensitivity. Despite extensive research on mast cells, the underlying pathophysiology of mast cell activation syndromes remains poorly understood. Research by V. Cao et al. (6) examined the relationship between autoantibody levels to type 1 interferon in mastocytosis patients and disease severity. In a separate study, P. Valent et al. (7) discovered that patients with systemic mastocytosis who carry HaT demonstrate a significantly higher prevalence of severe allergic symptoms. Systemic mastocytosis patients with HaT and IgE-dependent allergies are more likely to develop anaphylaxis and mast cell activation syndrome. G.E.-S. Batiha et al. (8) examined mast cell activation syndrome, COVID-19 severity, and post-COVID syndrome risk.

J. Czarny et al. (9) noted that the basis of drug treatment of cutaneous mastocytosis is first- and second-generation H1 antihistamines. These drugs reduce itching, hyperaemia and tingling sensation of the skin. P. Valent et al. (10) describe alternative remedies to combat severe progressive forms of systemic mastocytosis. Mastocytosis is a diverse condition with an inadequately understood pathogenesis; hence, treatment primarily focuses on symptomatic management. In addition, many patients have persistent forms of mastocytosis that are not amenable to existing treatments. Thus, despite the large number of studies conducted, the pathogenesis, and hence the treatment and prevention of disorders associated with tryptase metabolism, are poorly understood.

The work aimed to study and describe the effect of tryptase on the functioning of the human body under physiological and pathological conditions. Objectives of the paper are:

- describing the main properties and role of mast cells;
- studying the forms of tryptase;
- detailing the epidemiology, pathophysiology, clinical presentation, diagnosis, and management of the following conditions: systemic mastocytosis, cutaneous mastocytosis, hereditary alpha-tryptasemia, anaphylaxis, mast cell activation syndrome, and clonal mast cell activation syndrome;
- defining the principal characteristics of the association between elevated serum tryptase levels and PLCG2-associated antibody deficiency and immunological dysregulation (PLAID), GATA2 transcription factor deficient syndrome, and chronic kidney disease.

MATERIALS AND METHODS

In July 2024, a comprehensive systematic search examining the role of the tryptase enzyme in the human body was conducted. Our investigation spanned multiple databases including PubMed, ResearchGate, Scopus, Web of Science, and Google Scholar. We analyzed all available relevant literature published between 2014 and 2024 in peer-reviewed journals, encompassing clinical trials, randomized controlled trials, systematic reviews, and meta-analyses. The search included articles published in Polish, French, Spanish, German, and English languages to ensure maximum coverage of the existing research. The search was performed using the following queries: “tryptase”, “tryptase level is normal”, “measurement of tryptase level”, “tryptase isoforms”, “mast cells”, “hypersensitivity”, “anaphylactic reaction”, “mastocyte activation syndrome”, “systemic mastocytosis”, “epidemiology of mastocytosis”, “pathogenesis of mastocytosis”, “clinical manifestations of mastocytosis”, “diagnosis of mastocytosis”, “treatment of mastocytosis”, “prevalence of mastocyte activation syndrome”, “pathogenesis of mastocyte activation syndrome”, “symptoms of mastocyte activation syndrome”, “diagnosis of mastocyte activation syndrome”, “treatment of mastocyte activation syndrome”, “prevention of mastocyte activation syndrome”, “symptoms of anaphylaxis”, “diagnosis of anaphylaxis”, “treatment of anaphylaxis”, “complications of allergic reactions”, “emergency care in anaphylaxis”, “monoclonal mast cell activation syndrome”, “chronic kidney disease pathogenesis”, “GATA2 transcription factor deficiency syndrome”.

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The literature search yielded 1,800 papers which underwent rigorous review, processing, and analysis. Papers were initially selected based on title, abstract, relevance, publication date, and appropriate evidence level for the case studies. Duplicate papers and those falling outside the designated publication timeframe were excluded. All remaining articles were evaluated against predetermined inclusion and exclusion criteria, with immediate removal of papers that failed to meet these standards partially or fully. Articles containing outdated, unconfirmed, or irrelevant information were excluded from the study.

The final analysis incorporated works from 2014-2024, providing current information on tryptase's primary characteristics and effects on the human body in both physiological and pathological conditions, including details on tryptase types and the specific roles of each isoform. The study utilized data describing anaphylaxis, systemic mastocytosis, and mast cell activation syndrome without limitations regarding gender, age, race, geographic location, social status, or disease course and severity. Studies outlining emergency anaphylaxis care protocols were included, as were those presenting new findings on enzyme metabolism in basophils. This methodical selection process yielded 50 relevant articles fully meeting all required criteria. To ensure accuracy, all selected information sources underwent secondary evaluation, processing, and verification.

GENERAL CHARACTERISTICS OF MAST CELLS AND TRYPTASE

Mast cells originate from pluripotent progenitors in the bone marrow before migrating to peripheral tissues like the skin, lungs, and gastrointestinal tract where they complete their differentiation. Positioned at the interface between the body and the environment, these cells serve as crucial sentinels in the body's defense system. When activated, mast cells produce responses that vary significantly in intensity, determined by several factors: genetic background, the number and reactivity of mast cells in the affected area, characteristics of the triggering allergen and how it enters the body, the specific organ involved, and any existing comorbidities that may influence the reaction.

Mature mast cells contain granules with mediators (tryptase and histamine). They initiate and organize the immune response by attracting neutrophils, T cells and NK cells; enhance the effector functions of neutrophils through the release of chemokines; additionally promote the recruitment of neutrophils and T cells through inflammatory vasodilation, endothelial activation and connective tissue relaxation; modulate the functions of dendritic cells, promoting their migration and maturation, affecting immunity. Mast cells identify infectious pathogens and produce granules that impede bacterial proliferation (by phagocytosis and the secretion of antimicrobial peptides), exhibit cytotoxicity towards helminths, and enhance the permeability of the intestinal epithelial barrier. They aggregate around blood arteries and follicles (11, 12). If the normal functioning of mast cells (and, accordingly, their enzymes) is disrupted, they contribute to the development of a number of pathological conditions. They cause excessive fibrosis and the development of keloid scars; they cause vasoconstriction in poorly vascularized kidneys through the activation of angiotensin. Mast cells are involved in numerous pathological processes including transplant rejection, inflammatory bowel disease, atherosclerotic plaque progression, arthritis, osteoporosis, psoriasis, and both atopic and contact dermatitis. Tryptase serves as the predominant component of mast cells and functions as a standardized marker of their activity. Tryptase is a tetrameric neutral serine protease that functions by degrading proteins through polypeptide cleavage at the carboxy-terminal domain of arginine and lysine amino acids, or through indirect proteolysis. This enzyme is essential for the development and metabolism of mesenchymal cells, endothelial cells, and fibroblasts. It also exerts a significant influence on coagulation processes, connective tissue metabolism, angiogenesis, and the contractility of smooth muscle cells. The normal basal level of serum tryptase is approximately 5 ng/ml, with 11.4 ng/ml considered the threshold clinical value.

Tryptase tetramers are enzymatically active protein complexes with molecular weights up to 140 kDa, composed of four monomeric subunits. In the absence of systemic mast cell activation, monomeric pro-α-tryptase and pro-β-tryptase are secreted into tissues and subsequently diffuse into the bloodstream as the predominant forms. The biologically active mature α/β-tryptase heterotetramers consist of four non-covalently linked subunits that interact with two clinically significant targets: EGF-like factor containing mucin-like hormone receptor 2 (EMR2) and protease-activated receptor 2 (PAR2). Scientists have identified several tryptase isoforms, including alpha-1, alpha-2, beta-1, beta-2, beta-3, gamma, and epsilon-tryptase. In humans, tryptase is encoded by multiple genes located in the genomic region 16p13.3: tryptase alpha/beta (TPSAB1), which typically has 4 copies; gamma-tryptase (TPSG1); beta-tryptase (TPSB2); and ipsilon-tryptase (TPSD1). Functionally, tryptase is classified as a tetrameric neutral serine protease that breaks down proteins through polypeptide cleavage at the carboxy-terminal domain of arginine and lysine amino acids, or through indirect proteolysis. This enzyme plays essential roles in the development and metabolism of mesenchymal cells, endothelial cells, and fibroblasts. Additionally, tryptase influences critical physiological

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processes including coagulation, connective tissue metabolism, angiogenesis, and smooth muscle cell contractility (12-14).

HEREDITARY CAUSES OF TRYPTASE ELEVATION

Hereditary alpha-tryptase deficiency

This autosomal dominant disorder results from an elevation in germline copies of TPSAB1, which encodes alpha-tryptase (2). The epidemiology is about 5%. Hereditary alpha-tryptasemia is 2-3 times more common in systemic mastocytosis patients. The combination of hereditary alpha-tryptasemia with cutaneous mastocytosis is 7-12%, indolent CM 12%; smouldering CM 9%; and progressive CM 11%. This leads to a more severe course of mastocyte-mediated symptoms in these patients (15). Growth produces alpha/beta tryptase tetramers. These tetramers cut and activate PAR2 and EGF-like factor-containing mucin-like hormone receptors. When these receptors are activated, they make vascular oedema worse, which can cause hives, angioedema, and anaphylaxis.

Functional gastrointestinal issues, irritable bowel syndrome, and reflexes are the main symptoms. Skin signs include redness, itching, swelling, and urticaria. Patients develop connective:

- tissue abnormalities (joint hypermobility);
- autonomic dysfunction (orthostatic hypotension, palpitations, tachycardia, syncope);
- neuropsychiatric symptoms (fatigue, depression, sleep disorders, memory problems).

Eosinophilic diseases of the gastrointestinal tract, multiple food intolerances, and growth retardation are observed in children. In 20% of patients, the development of IgE-mediated immediate hypersensitivity due to Hymenoptera bites was described. The treatment of hereditary alpha-tryptasemia is to reduce symptoms. In case of gastrointestinal disorders, medications targeting H1-histamine receptors and H2-histamine receptors are prescribed (15, 16). PLCG2-related antibody deficiency and immune dysregulation (PLAID). The primary signs consist of cold urticaria (diagnosed during childhood), recurrent bacterial infections, autoimmune disorders, and the development of skin granulomas.

Cold urticaria

Cold urticaria is characterized by classic urticaria that occurs as a result of contact with cold material. As a result, mast cells are hyperactivated and degranulated, and serum tryptase levels increase accordingly. Triggers include exposure to cold air from air conditioners, cold water, and ice cream. Eating cold food provokes a burning sensation in the throat and behind the sternum. Symptoms of the disease appear within a few minutes and disappear after warming up. It is worth noting that prolonged systemic exposure to cold can lead to anaphylaxis. The standard for diagnosing this pathology is the appearance of urticaria after contact with an ice cube (17, 18). It is a genetic protein condition characterized by GATA2 haploinsufficiency, classified among myelodysplastic syndromes and immunodeficiency. It is the predominant etiology of primary myelodysplastic syndrome in pediatric patients. The manifestations include instability to viral and bacterial pathogens, lymphoedema, primary alveolar proteinosis, and increased tryptase in the blood. Patients have compromised mast cell activation attributable to GATA2 pathology, which is essential for the development of the stem cell factor receptor KIT and the high-affinity IgE receptor FcεRI. These individuals face a heightened risk of developing myeloid malignancies linked to elevated tryptase levels. Therefore, it is important to determine the level of this enzyme and to search for the causes of its increase in detail (19, 20).

ACQUIRED CAUSES OF TRYPTASE ELEVATION

Mastocytosis

General characteristics of mastocytosis. Pathological proliferation and aggregation of mast cells is indicative of the skin (cutaneous mastocytosis) and several organ systems, including the gastrointestinal tract, liver, and spleen (systemic mastocytosis). The epidemiology is 1 case per 10,000 people (21). The disease can occur at any age, with various symptoms (from mild manifestations to severe forms that reduce life expectancy). It is categorized as cutaneous mastocytosis and systemic mastocytosis. Systemic mastocytosis is categorized as indolent systemic mastocytosis (ISM), smoldering systemic mastocytosis (SSM), systemic mastocytosis with associated hematological neoplasm (SM-AHN), aggressive systemic mastocytosis (ASM), and mastocytic leukemia (MCL). Patients with ISM exhibit a more favorable prognosis and typical life expectancy in contrast to individuals diagnosed with SM-ANH, ASM, or MCL.

Tissue mast cells proliferate and secrete tryptase, histamine, cytokines, and chemokines, causing mastocytosis. KIT-D816V activating mutations account for 85-90% of cases. When tryptase, histamine, prostaglandins, and leukotrienes bind to tissue receptors, they trigger the characteristic symptoms including localized redness, dizziness, hypotension, headache, and anaphylaxis. Interestingly, mediator levels don't consistently correlate with symptom severity. Both specific and non-specific triggers can activate mast cells, including NSAIDs, opiates, antibiotics, neuromuscular

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blockers, vaccines, and insect venoms. Hymenoptera stings induce anaphylactic shock in 30% of mastocytosis patients compared to 9% in the normal population (22). The overall prevalence of anaphylaxis among mastocytosis patients ranges from 20-50%, with 75% of these patients experiencing loss of consciousness during anaphylactic episodes.

P. Bonadonna et al. (23) indicated that 11% of patients with mastocytosis had adverse reactions (including anaphylaxis) in response to NSAIDs. Most symptoms (90%) were localized to the skin. T.A. Rama et al. (24) reported that the main triggering NSAIDs were aspirin (17%), metamizole (12%) and coxibs (12%). D. Sarcina et al. (25) reported a 1.5-year-old boy with cutaneous mastocytosis who developed a significant bullous skin reaction one day after receiving the second inactivated tetravalent influenza vaccination. Systemic mastocytosis. Among adults, the most common form is indolent mastocytosis. This condition has a positive prognosis and does not impact patients' life expectancy. Concurrently, individuals with this diagnosis exhibit an elevated risk of getting melanoma. They occasionally have mastocytosis with haematological neoplasms, severe systemic mastocytosis, and mast cell leukaemia. Acute attacks last from 15 to 30 minutes on average. Patients complain of fever, palpitations, dizziness, and hypotension caused by systemic vasodilation, which leads to syncope (26).

Mediators include histamine, platelet-activating factor, prostaglandin, serotonin, tryptase, leukotrienes, TNF-alpha, and interleukin 6 cause gastrointestinal discomfort. The incidence of these symptoms is 75%. Under physiological conditions, mast cells in the intestine make up about 4% of mononuclear cells in the lamina propria (26). Normally, mast cells are evenly scattered throughout the intestinal mucosa, but in patients with systemic mastocytosis, they form conglomerates. That is, the symptoms of intestinal damage are the result of massive pathological release of mediators, which causes hypermotility, abdominal distension, diarrhoea, abdominal cramps, nausea, and vomiting; and the result of direct infiltration of the intestinal mucosa by neoplastic mast cells, which contributes to impaired absorption and weight loss (26).

Bloating and diarrhoea represent the most common symptoms of mastocytosis, with nausea, abdominal pain, and vomiting occurring less frequently (27, 28). Patients suffering from this condition face an elevated risk of developing peptic ulcers because heightened histamine levels trigger excessive gastric acid secretion. Diagnosis confirmation relies on specific criteria. The primary criterion involves identifying mast cell aggregates (exceeding 15 cells per cluster) in biopsy sections (27). The diagnostic criteria for systemic mastocytosis include bone marrow biopsies showing mast cell aggregates exceeding 25% of the sample. These cells often exhibit spindle morphology or atypical features (26). The presence of the activating KIT-D816V mutation in bone marrow, blood, or affected organs provides molecular confirmation. Flow cytometry revealing aberrant clonal mast cells that express CD117 along with CD25, CD2, and/or CD30 in bone marrow, peripheral blood, or extracutaneous organs further supports the diagnosis. Elevated baseline serum tryptase levels measuring 20 ng/ml or higher represent another characteristic finding (27). For treatment, researchers have developed multiple tyrosine kinase inhibitors specifically targeting the KIT-D816V mutation in patients with systemic mastocytosis (26). Midostaurin and avapritinib, for instance, slow disease progression and reduce non-neoplastic mast cell numbers, serving as first-line treatments for advanced systemic mastocytosis. Research indicates avapritinib induces hematological remission in patients with advanced forms of the disease (26).

T. Sun and M. Xavier (29) documented omalizumab's effectiveness in systemic mastocytosis cases. Additionally, L. Kibsgaard et al. (30) reported complete anaphylaxis remission following omalizumab therapy in a young man with indolent systemic mastocytosis. However, comprehensive randomized trials investigating this approach remain lacking (11). Imatinib mesylate has received approval for treating aggressive systemic mastocytosis without the D816V KIT mutation or when mutation status remains unknown. Its primary limitation lies in its restricted applicability, as most patients carry the D816V KIT mutation. Interferon-α (IFN-α) stands as a first-line cytoreductive option for symptomatic systemic mastocytosis, particularly indicated for cases involving ASM with liver damage and ascites (9). It's also recommended for patients experiencing rapidly progressive ASM or undergoing polychemotherapy (31). Cutaneous mastocytosis manifests in several forms: cutaneous mastocytoma, diffuse cutaneous mastocytosis, and maculopapular cutaneous mastocytosis (which includes both polymorphic and monomorphic variants) (32, 33).

In children, the main forms are mastocytoma and polymorphic cutaneous mastocytosis. Most children have few symptoms. By the age of 6 months, a reddish-brown itchy rash appears. Due to pressure on the affected skin area (diaper), the epidermis and dermis become separated, which leads to blistering. In general, the course and prognosis of cutaneous mastocytosis in children is favourable, with a gradual regression of symptoms during puberty. At the same time, children with maculopapular cutaneous mastocytosis of monomorphic type have a risk of chronic course. Mastocytoma is the most common and benign. It is characterized by a local, single, well-defined yellow-brown infiltrate up to several centimetres in size.

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Upon mechanical injury, the rash exhibits edema and blister development. J. Cernova et al. (32) documented a case of a sizable solitary congenital mastocytoma in a neonate. The size of the lesion was 13 by 6 cm, had the appearance of large bullae and erosions, and was located on the thigh. Skin samples revealed monomorphic CD117 (c-KIT) positive infiltration, which confirmed the diagnosis of cutaneous mastocytoma.

Maculopapular cutaneous mastocytosis manifests as red-brown maculopapules and plaques that vary in size. These skin lesions typically appear on the neck, head, trunk, and proximal extremities, though facial involvement is uncommon. The quantity of rashes varies from several to hundreds. Diffuse cutaneous mastocytosis is a severe but rare pathology (34). It affects the entire skin and is characterized by the appearance of reddish-yellow cobblestone-like thickenings. In adults, the skin lesions begin in adolescence and last until the age of 35. The rash is localized on the thighs and lower trunk, rarely spreading to the face. On examination, there are smooth or slightly raised brownish-red lesions up to 2-5 mm. The number of rash elements ranges from 10 to 100, and they can coalesce. In 10% of people, the rash disappears by the age of 40. The diagnosis includes the presence of Darien's symptom (redness due to scraping the affected area with a spatula). This is a pathognomonic symptom, it differs from cutaneous dermatography in that the reaction is limited to the affected skin area. It is worth noting that the described symptom is typical for childhood, so in adults, a biopsy of the skin area is performed for examination. Immunohistochemistry is performed using antibodies against tryptase. The number of dermal mast cells in cutaneous mastocytosis is 5-10 times higher than in normal skin.

The main goal of treatment is symptom control, so histamine receptor antagonists are the drugs of choice for cutaneous mastocytosis. Skin symptoms such as itching, flushing and burning sensation are controlled with 1st and 2nd generation H1 antihistamines. In case of ineffectiveness of this therapy, H2 antihistamines and leukotriene antagonists (montelukast) are added. It is worth noting that H2 antihistamines are the drugs of choice for gastrointestinal symptoms: abdominal pain, cramps, diarrhoea and gastric hypersecretion. Pediatric mastocytosis primarily presents as skin conditions that are often temporary (35, 36). For children with symptomatic mastocytoma, doctors may prescribe topical glucocorticoids for brief treatment periods. While topical glucocorticoids effectively reduce skin manifestations and improve appearance, their use should be strictly limited to short durations due to their numerous potential side effects. These adverse effects include skin thinning, visible blood vessels, abnormal pigmentation (both darker and lighter), bone mineral loss, and suppression of adrenal function. In cases involving severe blistering skin lesions, systemic glucocorticosteroids may be prescribed. However, these medications carry significant systemic risks, including diabetes, hypertension, osteoporosis, immunosuppression, heart disease, and Cushing's syndrome.

Phototherapy results in a partial alleviation of skin lesions and a decrease in pruritus (37). However, this method is not widely used due to the carcinogenic effect of prolonged use. In addition, phototherapy is inappropriate in children due to the self-limiting course of mastocytosis in childhood. Phototherapy and photochemotherapy in the elderly demonstrate limited efficacy, resulting in only transient and partial amelioration of dermatological signs and symptoms (38-40). Patients report recurring anaphylactic episodes accompanied by cardiovascular manifestations (hypotension, syncope) without the presence of urticaria. The mast cell count is either normal or marginally elevated. The serum tryptase level is 10-20 ng/ml. There are no skin manifestations characteristic of mastocytosis. Criteria, compiled by the author based on (41-43), have been developed to make the diagnosis:

- KIT-D816 bone marrow or extracutaneous organ mutation
- Abnormal clonal mast cells expressing CD117 with CD25, CD2, or CD30 in bone marrow, peripheral blood, or extracutaneous organs

Treatment is aimed at reducing the symptoms of the disease (41-43).

Mast cell activation syndrome (MCAS)

Mast cell activation syndrome (MCAS) includes clonal and nonclonal haematopoietic system diseases. The condition has a significant prevalence, affecting approximately 15-18% of the population (44). Research by G.E.-S. Batiha et al. (8) demonstrated that MCAS development during SARS-CoV-2 infection correlates directly with COVID-19 severity and subsequent post-COVID syndrome manifestation. Similarly, L.B. Afrin et al. (45) observed that cytokine storms in COVID-19 patients resulted from MCAS progression triggered by SARS-CoV-2 infection. The unregulated release of inflammatory mediators in MCAS can lead to post-COVID syndrome.

Clonal mast cell disease patients have higher serum tryptase levels, KITD816V mutations in mast cells, and abnormal CD25 expression. These findings indicate primary MCAS, with a definitive diagnosis requiring bone marrow biopsy. The distinguishing characteristic of nonclonal MCAS is the normal quantity and morphology of mast cells. For an accurate diagnosis, tryptase measurements should be obtained within four hours of

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Table 1. Diagnostic criteria for anaphylaxis

1	2	3
Acute onset of the disease with typical allergic skin and mucous membrane lesions; respiratory (hypoxia, shortness of breath, wheezing) and cardiovascular (hypotension, fainting) disorders.	Symptoms of damage to 2 or more of the following systems: integumentary, respiratory, cardiovascular, gastrointestinal.	Hypotension after contact with an allergen.

Source: compiled by the author based on (12, 39).

suspected mast cell activation episodes (47, 48). MCAS treatment approaches include antihistamines (H1 and H2 receptor antagonists), mediator synthesis inhibition (aspirin), mediator release inhibition, and prevention of mast cell degranulation. Chronic kidney disease (CKD) is diagnosed by a lower glomerular filtration rate and kidney structural or functional abnormalities lasting at least three months (49, 50). Male CKD patients had greater serum tryptase levels than females. Notably, enzyme concentrations were elevated in advanced CKD (stages 4 and 5) and in patients undergoing hemodialysis, contrasting with the lower levels observed in early-stage CKD patients (stages 1 and 2) (48, 51, 52).

Tryptase triggers the protease-activated receptor-2 (PAR-2), a member of the G-protein coupled receptor family. This receptor is extensively distributed across the kidneys, with particular concentration in tubular epithelial cells. When activated, PAR-2 initiates inflammatory and fibrotic mechanisms in injured kidney tissue (53). PAR-2 is found in various kidney structures including podocytes, epithelial tubules, mesangial cells, collecting duct cells, as well as inflammatory and fibroblastic cells. Notably, PAR-2 can transactivate TGF-β receptors, which are key regulators of renal fibrosis (54). Within the kidneys, TGF-β promotes profibrotic conditions through direct activation of chronic inflammatory cells and indirect promotion of epithelial-to-mesenchymal transition, while also inducing apoptosis in endothelial cells and podocytes (55, 56). Studies of biopsy samples from IgA nephropathy patients reveal elevated PAR-2 levels compared to normal kidney tissue (54). These samples also show increased mast cell infiltration, primarily localized in the interstitial spaces. The degree of infiltration correlates with elevated serum creatinine levels and interstitial fibrosis in IgA nephropathy. Patients presenting with more severe renal disease typically demonstrate higher levels of mast cell infiltration, whereas those with preserved kidney function show reduced presence of these cells.

Anaphylaxis

Anaphylaxis represents an acute systemic hypersensitivity reaction classified as Type 1. Systemic mastocytosis is a widespread disorder characterized by excessive activation of mast cells throughout the body, leading to the release of large quantities of chemical mediators that cause severe symptoms (57). The condition involves both IgE-mediated and non-IgE-mediated pathways. According to European epidemiological studies, the incidence ranges from 2 to 8 cases per 100,000 person-years. The main triggers in children are allergenic foods (90% of cases), and in adults, hymenopteran venom and drug intolerance. Deaths occur with a frequency of 1 per 30,000,000 population per year. Mortality among children is rare, occurring more often in adults due to cardiovascular failure (54). The development of anaphylaxis occurs rapidly, with the involvement of several organ systems simultaneously. A rise in serum tryptase above baseline indicates mast cell activation in severe anaphylactic and systemic hypersensitivity events. In healthy individuals, with the development of anaphylactic shock, tryptase levels reach 100 ng/ml within 1 hour of onset (58, 59).

A number of criteria have been developed for accurate diagnosis and differential diagnosis with allergy (Table 1). These criteria have a sensitivity of 95% and a specificity of 70%. Treatment consists of emergency care using an intramuscular epinephrine solution.

CONCLUSIONS

Serum tryptase serves as an important biomarker for evaluating mast cell activity. In healthy individuals, enzyme levels typically measure around 5 ng/ml, with 11.4 ng/ml established as the clinical threshold. Tryptase plays multiple physiological roles, including influencing the growth and development of mesenchymal cells, fibroblasts, and endothelial cells. Various clinical conditions are associated with mast cell degranulation and subsequent tryptase release, including allergic reactions, anaphylaxis, mastocytosis, hereditary alpha-tryptasemia, mast cell activation syndromes, monoclonal mast cell activation syndrome, and chronic kidney disease. These conditions typically manifest with symptoms affecting the cardiovascular, gastrointestinal, respiratory, excretory, and integumentary systems, potentially leading to anaphylaxis. Currently, treatment approaches for many of these conditions remain investigational.

Individuals with elevated serum tryptase levels face increased risk of anaphylactic reactions to Hymenoptera stings and higher susceptibility to myeloid diseases. Patients diagnosed with systemic mastocytosis who also have hereditary alpha-tryptasemia and IgE-dependent allergies show heightened vulnerability to

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anaphylaxis and mast cell activation syndrome. The concurrent presentation of multiple mast cell disorders in a single patient often complicates clinical management, elevates mortality risk, and diminishes overall quality of life. Mast cell activation syndromes can exacerbate infectious disease progression. Post-COVID syndrome may be influenced by the dysregulated release of mediators in mast cell activation syndrome. A major limitation in research is our incomplete understanding of how mast cell activation syndrome develops. We need further research into the mechanisms behind mastocytosis, hereditary alpha-tryptasemia, mast cell activation syndrome, monoclonal mast cell activation syndrome, chronic kidney disease, PLCG2-associated antibody deficiency and immune dysregulation, and GATA2 transcription factor deficiency syndrome to develop effective prevention strategies and treatments.

REFERENCES

1. Szudy-Szczyrek A, Bachanek-Mitura O, Gromek T, et al. Real-world efficacy of midostaurin in aggressive systemic mastocytosis. J Clin Med 2021; 10: 1109.
2. Glover SC, Carter MC, Korošec P, et al. Clinical relevance of inherited genetic differences in human tryptases: Hereditary alpha-tryptasemia and beyond. Ann Allergy Asthma Immunol 2021; 127: 638–47.
3. Valent P, Akin C, Hartmann K, et al. Updated diagnostic criteria and classification of mast cell disorders: A consensus proposal. Hemasphere 2021; 5: e646.
4. Kozyra EJ, Pastor VB, Lefkopoulos S, et al. Synonymous GATA2 mutations result in selective loss of mutated RNA and are common in patients with GATA2 deficiency. Leukemia 2020; 34: 2673–87.
5. Shea J, Huynh T, Milner J, Chamlin S. PLAID syndrome: Characteristic presentation and a novel therapeutic option. Pediatr Dermatol 2020; 37: 147–9.
6. Cao V, Lee S, Bai Y, et al. Autoantibodies to type I interferons in patients with systemic mastocytosis. J Allergy Clin Immunol Glob 2024; 3: 100273.
7. Valent P, Hartmann K, Bonadonna P, et al. Mast cell activation syndromes: Collegium Internationale Allergologicum update 2022. Int Arch Allergy Immunol 2022; 183: 693–705.
8. Batiha GE-S, Al-Kuraishy HM, Al-Gareeb AI, Welson NN. Pathophysiology of post-COVID syndromes: a new perspective. Virol J 2022; 19: 158.
9. Czarny J, Lange M, Ługowska-Umer H, Nowicki RJ. Cutaneous mastocytosis treatment: Strategies, limitations and perspectives. Adv Dermatol Allergol 2018; 35: 541–5.
10. Valent P, Akin C, Arock M, et al. Antibody-based and cell therapies for advanced mastocytosis: Established and novel concepts. Int J Mol Sci 2023; 24: 15125.
11. Mihele DM, Nistor PA, Bruma G, et al. Mast cell activation syndrome update – a dermatological perspective. J Pers Med 2023; 13: 1116.
12. Sprinzl B, Greiner G, Uyanik G, et al. Genetic regulation of tryptase production and clinical impact: Hereditary alpha tryptasemia, mastocytosis and beyond. Int J Mol Sci 2021; 22: 2458.
13. Dileepan KN, Raveendran VV, Sharma R, et al. Mast cell-mediated immune regulation in health and disease. Front Med (Lausanne) 2023; 10: 1213320.
14. Palmer RF, Dempsey TT, Afrin LB. Chemical intolerance and mast cell activation: a suspicious synchronicity. J Xenobiot 2023; 13: 704–18.
15. von Bubnoff D, Koch D, Stocker H, et al. The clinical features of hereditary alpha-tryptasemia. Dtsch Arztebl Int 2024; 121: 258–64.
16. Kranyak A, Shuler M, Lee LW. Cutaneous manifestations in hereditary alpha tryptasemia. Cutis 2023; 111: 49–52.
17. Aderibigbe OM, Priel DL, Lee CC, et al. Distinct cutaneous manifestations and cold-induced leukocyte activation associated with PLCG2 mutations. JAMA Dermatol 2015; 151: 627–34.
18. Schade A, Walliser C, Wist M, et al. Cool-temperature-mediated activation of phospholipase C-γ2 in the human hereditary disease PLAID. Cell Signal 2016; 28: 1237–51.
19. Fujiwara T. GATA transcription factors: Basic principles and related human disorders. Tohoku J Exp Med 2017; 242: 83–91.
20. Chang Y, Hummel SN, Jung J, et al. Engineered hematopoietic and immune cells derived from human pluripotent stem cells. Exp Hematol 2023; 127: 14–27.
21. Giannetti MP, Nicoloro-SantaBarbara J, Godwin G, et al. Challenges in drug and hymenoptera venom hypersensitivity diagnosis and management in mastocytosis. Diagnostics (Basel) 2024; 14: 123.
22. Carter MC, Metcalfe DD, Matito A, et al. Adverse reactions to drugs and biologics in patients with clonal mast cell disorders: A Work Group Report of the Mast Cells Disorder Committee, American Academy of Allergy, Asthma & Immunology. J Allergy Clin Immunol 2019; 143: 880–93.
23. Bonadonna P, Olivieri F, Jarkvist J, et al. Non-steroidal anti-inflammatory drug-induced anaphylaxis is infrequent in 388 patients with mastocytosis: a two-centre retrospective cohort study. Front Allergy 2022; 3: 1071807.

doi: 10.5937/mckg59-55869
COBISS . SR - ID 173831433
UDK. 577.151.4

24. Rama TA, Morgado JM, Henriques A, et al. Mastocytosis presenting with mast cell-mediator release-associated symptoms elicited by cyclooxygenase inhibitors: prevalence, clinical, and laboratory features. Clin Transl Allergy 2022; 12: e12132.
25. Sarcina D, Giovannini M, Oranges T, et al. Case report and review of the literature: bullous skin eruption after the booster-dose of influenza vaccine in a paediatric patient with polymorphic maculopapular cutaneous mastocytosis. Front Immunol 2021; 12: 688364.
26. Zanelli M, Pizzi M, Sanguedolce F, et al. Gastrointestinal manifestations in systemic mastocytosis: the need of a multidisciplinary approach. Cancers (Basel) 2021; 13: 3316.
27. Pardanani A. Systemic mastocytosis in adults: 2021 update on diagnosis, risk stratification and management. Am J Hematol 2021; 96: 508–25.
28. Kerashvili S, Slonetsky B, Maksimenko M, et al. Some features of the modeling and age differences of the course of acute experimental peritonitis. Georg Med News 2013; 214: 67–73.
29. Sun T, Xavier M. A case of indolent systemic mastocytosis responding to treatment with Avapritinib. Clin Case Rep 2024; 12: e8500.
30. Kibsgaard L, Skjold T, Deleuran T, Vestergaard C. Omalizumab induced remission of idiopathic anaphylaxis in a patient suffering from indolent systemic mastocytosis. Acta Derm Venereol 2014; 94: 363–4.
31. Bergström A, Rollman O, Emtestam L, et al. Cutaneous mastocytosis - update and clinical guidelines. Lakartidningen 2018; 115: FASY. (in Swedish).
32. Cernova J, Patel M, Ligaj M, et al. Large congenital cutaneous mastocytoma presenting with recurrent persistent blistering: a case report. Cureus 2023; 15: e50306.
33. Hartmane I, Ivdra I, Mikaþâns I, et al. Correlation of immunological and clinical changes in psoriasis patients treated with tumour necrosis factor-alpha (TNF-α) blocking biologic drugs: one-year dynamic observation. Proceed Latv Acad Sci Sect B Nat Exact Appl Sci 2021; 75: 357–63.
34. Yermukhanova L, Buribayeva Z, Abdikadirova I, et al. SWOT analysis and expert assessment of the effectiveness of the introduction of healthcare information systems in polyclinics in Aktobe, Kazakhstan. J Prev Med Publ Health 2022; 55: 539–48.
35. Ravshanov AX, Suhail M, Komilova N, et al. Medical geographical zoning in part of Uzbekistan - a regional synthesis. Reg Sci Pol Pract 2024; 16: 100142.
36. Komilova N, Karshibaeva L, Egamberdiyeva U, et al. Territorial Analysis of the nosoecological situation and the health of the population of the Syrdarya region. Univ J Publ Health. 2024; 12: 207-17.
37. Hartmane I, Ivdra I, Mikazans I, et al. Immunopathogenic treatment options for psoriasis patients under a restrictive reimbursement environment. Proceed Latv Acad Sci Sect B Nat Exact Appl Sci 2021; 75: 158–66.
38. Romantowski J, Górska A, Lange M, et al. How to diagnose mast cell activation syndrome: practical considerations. Pol Arch Intern Med 2020; 130: 317–23.
39. Gülen T, Akin C. Anaphylaxis and mast cell disorders. Immunol Allergy Clin North Am 2022; 42: 45–63.
40. Zmorzynski S, Kimicka-Szajwaj A, Szajwaj A, et al. Genetic changes in mastocytes and their significance in mast cell tumour prognosis and treatment. Genes (Basel) 2024; 15: 137.
41. Jarkvist J, Salehi C, Akin C, Gülen T. Venom immunotherapy in patients with clonal mast cell disorders: IgG4 correlates with protection. Allergy 2020; 75: 169–77.
42. Arun S, Storan A, Myers B. Mast cell activation syndrome and the link with long COVID. Br J Hosp Med (Lond) 2022; 83: 1–10.
43. Johnson-Weaver B, Choi HW, Abraham SN, Staats HF. Mast cell activators as novel immune regulators. Curr Opin Pharmacol 2018; 41: 89–95.
44. Gülen T. A puzzling mast cell trilogy: anaphylaxis, MCAS, and mastocytosis. Diagnostics (Basel) 2023; 13: 3307.
45. Afrin LB, Weinstock LB, Molderings GJ. Covid-19 hyperinflammation and post-Covid-19 disease may be rooted in mast cell activation syndrome. Int J Infect Dis 2020; 100: 327–32.
46. Weinstock LB, Pace LA, Rezaie A, Afrin LB, Molderings GJ. Mast cell activation syndrome: a primer for the gastroenterologist. Dig Dis Sci 2021; 66: 965–82.
47. Hamilton MJ. Mast cell activation syndrome and gut dysfunction: diagnosis and management. Curr Gastroenterol Rep 2024; 26: 107–14.
48. Owens E, Tan KS, Ellis R, et al. Development of a biomarker panel to distinguish risk of progressive chronic kidney disease. Biomedicines 2020; 8: 606.
49. Dostanova Z, Yermukhanova L, Blaževičienė A, et al. Perception and experience of independent consultations in primary healthcare among registered nurses in Kazakhstan: a qualitative study. Healthcare Switz 2024; 12: 1461.

doi: 10.5937/mckg59-55869
COBISS . SR - ID 173831433
UDK. 577.151.4

50. Dobrovanov, O.Y. Efficacy and sensitivity of prenatal and postnatal ultrasound screening of congenital developmental anomalies of kidneys in Slovakia. Wiad Lek Wars Pol 1960 2021; 74: 450–4.
51. Owens EP, Vesey DA, Kassianos AJ, et al. Biomarkers and the role of mast cells as facilitators of inflammation and fibrosis in chronic kidney disease. Transl Androl Urol 2019; 8(Suppl 2): S175–S183.
52. Cao Y, Du Y, Jia W, et al. Identification of biomarkers for the diagnosis of chronic kidney disease (CKD) with non-alcoholic fatty liver disease (NAFLD) by bioinformatics analysis and machine learning. Front Endocrinol (Lausanne) 2023; 14: 1125829.
53. Tomasz O, Waldemar K, Kajetan Ł, et al. Robotics in neurosurgery – past, presence and future. Adv Intell Syst Comp 2021; 1362: 1–8.
54. Lobbes H, Reynaud Q, Mainbourg S, et al. Tryptase: a practical guide for the physician. Rev Med Interne 2020; 41: 748–55.
55. Matyushin N, Ermakov D, Vasileva I, et al. Investigating kidney function changes in young adults with COVID-19: serum creatinine level, glomerular filtration rate, and biochemical profile analysis. Elect J Gen Med 2023; 20: em547.
56. Dobrovanov O, Králinský K. Sonographic screening of congenital kidney malformations in Slovakia. Lek Obz 2018; 67: 426–9.
57. Efremov A. Psychosomatics: Communication of the central nervous system through connection to tissues, organs, and cells. Clin Psychopharm Neurosci 2024; 22: 565-77.
58. Gharote H, Bhowate R, Dangore-Khasbage S. Enzyme-linked immunosorbent assay and immunohistochemical analysis of mast cell related biochemicals in oral submucous fibrosis. F1000Res 2024; 12: 1288.
59. Poto R, Marone G, Galli SJ, Varricchi G. Mast cells: a novel therapeutic avenue for cardiovascular diseases? Cardiovasc Res 2024; 120: 681–98.