

# Histamine intolerance (HIT)

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## ABSTRACT

Histamine intolerance (HIT) is food intolerance of non-immunological origin, and it results from an imbalance between the consumption of histamine with food and the organism ability to metabolize it. The patients with HIT were found to have a significantly reduced concentration of histamine-degrading enzymes, diamine oxidase (DAO) and histamine N-methyltransferase (HNMT). Factors which have been identified that are conducive to histamine intolerance are: genetic factors, dysbacteriosis, chronic diseases – especially allergic and intestinal diseases, chronic infections, mastocytosis and some drug use. Clinical symptoms of histamine excess may affect various organs and systems - the most common are skin symptoms (pruritis, erythema) nausea, vomiting, abdominal pain, diarrhea, headaches and sometimes severe reactions with shortness of breath, arrhythmias, blood pressure drop, and even cardiac arrest.

Diagnostic methods in HIT utilize determination of serum DAO, determination of histamine metabolites in urine, measurement of the histamine wheal in the 50th minute of the skin prick test (SPT), gastroscopy with intestinal biopsy, diagnostic and therapeutic test, oral histamine-challenge test and genetic tests.

The mainstay of histamine intolerance treatment is a low-histamine diet. Patients should avoid products belonging to the three groups of food: containing large amounts of histamine, histamine liberators, and products inhibiting the activity of DAO. Additionally, supplements containing DAO and antihistamines can be used.

## Introduction

Histamine intolerance is food intolerance of non-immunological origin, and it results from an imbalance between the consumption of histamine with food and the organism ability to metabolize it [1]. In recent years, there has been a significant increase in the reported frequency of adverse food reactions. More and more patients come to the doctor for diagnosis or perform tests on their own. The most common tests are for food allergy or lactose intolerance. Meanwhile, in many patients it is not possible to make a proper diagnosis on their basis. Therefore, this article

discusses a very important issue regarding the histamine intolerance reaction. More attention by clinicians should be paid how challenging objective diagnosis of histamine intolerance is due to lacking reliable laboratory test or biomarkers and clear diagnostic criteria as well. According to the latest data, the disorder may affect up to 3%–6% of the population and is more common in children than in adults (the percentage given is for HIT only, not for food intolerance in general). [2, 3]. The patients with HIT were found to have a significantly reduced concentration of histamine-degrading enzymes, diamine oxidase (DAO) and histamine N-methyltransferase (HNMT). As the symptoms

of histamine intolerance are very similar to those of an allergic reaction, the term pseudoallergy is often used for HIT. Contrary to allergic reactions, in which even the smallest amount of the allergen can cause severe systemic symptoms, in patients with histamine intolerance, the severity of symptoms depends on the amount of histamine consumed with food. Current diagnostic methods utilize for example determination of serum DAO, determination of histamine metabolites in urine, measurement of the histamine wheal in the 50th minute of the skin prick test (SPT), and genetic tests. The mainstay of treatment is a low histamine diet, the use of antihistamines, and supplements containing DAO.

## Factors predisposing to HIT

So far, many factors have been identified that are conducive to histamine intolerance. These include:

- › genetic factors – histamine intolerance is most often associated with a single-nucleotide polymorphism (SNP) in the DAO gene that limits the production of the resulting protein [4];
- › dysbacteriosis – disturbances of the intestinal bacterial flora may lead to increased concentrations of histamine [5]. Some bacteria can produce and secrete histamine, and significant disturbances of the intestinal microflora have been found in patients with HIT [6];
- › other chronic diseases – especially allergic (atopic dermatitis, allergic rhinitis, asthma) [7, 8] and intestinal diseases (large intestine polyps, food allergies, celiac disease) [9]. Moreover, HIT is more common in patients with chronic infections and mastocytosis;
- › drug use – DAO activity is lowered by: mucocactive agents (ambroxol, acetylcysteine), antiemetics (metoclopramide), antidepressants (amitriptyline), anti-arrhythmic drugs, antihypertensive drugs (dihydralazine), and clavulanic acid [10].

## Symptoms of histamine intolerance

Histamine is a biogenic amine normally present in the human body. It is synthesized and secret-

ed by many cells, most importantly by mast cells and basophils. Accumulation of histamine, both exogenous and endogenous, can cause a variety of symptoms. The amine affects the cells via several known subtypes of histamine receptors [11].

H1 receptors are found primarily in the endothelium, airway smooth muscle, skin, and subcutaneous tissue. H2 receptors are located in mucosa and epithelium cells, immune cells and smooth muscle, and are involved in, inter alia, secretion of gastric juice. H3 receptors are found in the nervous system, and H4 ones in various cells of the immune system. Therefore, clinical symptoms of histamine excess may affect various organs and systems [12, 13]. The most common symptoms include:

- › skin symptoms – typically pruritis, erythema (often sudden facial erythema), hives, and edema;
- › gastrointestinal symptoms – nausea, vomiting, abdominal pain, diarrhea;
- › respiratory symptoms – runny nose, nasal mucosa swelling, shortness of breath;
- › nervous system symptoms – very frequent headaches, including migraine;
- › circulatory symptoms – arrhythmias, blood pressure drop, and even cardiac arrest [12].

The severity of HIT symptoms depends directly on the concentration of accumulated histamine. The concentration of 1–2 ng/ml increases the secretion of gastric juice and heart rate, and induces skin erythema. The level of 3–5 ng/ml causes headache, pruritis, hives, and tachycardia. At 7–12 ng/ml bronchospasm and dyspnea can occur, and histamine concentrations above 100 ng/ml cause cardiac arrest [10].

## Histamine-rich foods and histamine-releasing foods

Symptoms of histamine intolerance result from an imbalance between the excess of exogenous and/or endogenous histamine and the body ability to degrade it.

The foods that cause HIT are divided into three groups: the first group includes foods that contain large amounts of histamine, the second are foods that cause increased release of histamine from cells (so-called histamine liberators), and the third group comprises foods that are natural DAO inhibitors [14, 15].

Foods rich in histamine include: fish and seafood, ripened cheeses (e.g. parmesan), ripened meats (salami, skilandis), pickles (sauerkraut), fresh yeast and their extracts, some fruit and vegetables (tomato, spinach, eggplant, avocado).

Histamine liberators include: some fruit and vegetables (strawberries, raspberries, papaya, citrus fruit, spinach, eggplant, tomato, asparagus), alcohol (wine, champagne, beer), coffee, tea, cocoa, chocolate, nuts, and egg white.

The DAO inhibitors include: fish, cured meats, and sauerkraut.

## HIT diagnostics

HIT diagnosis is based on a detailed medical history of the patient ailments and their possible relationship with the consumed food. It may be helpful if the patient keeps a diary and notes down their symptoms and menu. A detailed history is also necessary regarding chronic diseases that may accompany HIT. Physical examination should assess clinical symptoms of histamine intolerance and accompanying conditions.

Additional tests helpful in HIT diagnosis:

- › determination of serum concentration and activity of DAO (ELISA) Currently, DAO enzyme activity in serum is the most studied but still controversial laboratory diagnostic approach and cannot be considered conclusive, mainly because level in serum doesn't entirely correspond to level in intestinal tissue. However there are some studies, that confirm the concentration and activity of DAO are statistically significantly lower in patients with histamine intolerance [16];
- › histamine 50 – skin-prick test – this is the assessment of the histamine wheal after a 50-minute skin prick test (SPT). A wheal with a diameter  $\geq 3$  mm is considered as denoting HIT [17]. Sensitivity of this test is 79 % and its specificity is 81%. SPT should always be performed to confirm or rule out possible IgE-mediated allergy, which manifests itself similarly to histamine intolerance, and these two conditions may overlap in many patients;
- › gastroscopy with intestinal biopsy – determination of intestinal concentration of DAO is a highly sensitive and specific method. Its

disadvantages include invasiveness and high costs [18];

- › determination of histamine and its metabolites in urine – a convenient and non-invasive method involving UHPLC-FL chromatography. In the future it may become a routine test used in everyday practice [19];
- › diagnostic and therapeutic test – in patients suspected of HIT, a physician may recommend a low-histamine diet or DAO supplementation for four to eight weeks. If clinical symptoms significantly cease or disappear, the test can be considered one of the criteria confirming histamine intolerance [20];
- › oral histamine-challenge test – consists in administering a solution containing 75 mg of histamine and observing clinical symptoms. The test may trigger severe systemic symptoms and must be performed in hospital conditions. Due to its low specificity (possible positive results in healthy people), this test is not recommended in the diagnosis of HIT [21];
- › determination of serum histamine concentration – currently not used in routine workup due to high cost and low availability [22];
- › genetic testing of DAO and HNMT SNPs in blood or oral mucosa samples. These tests are not an element of routine diagnosis.

## Treatment

The mainstay of histamine intolerance treatment is a low-histamine diet. Patients should avoid products belonging to the three groups mentioned above, that is those containing large amounts of histamine, histamine liberators, and products inhibiting the activity of DAO [23, 24].

Additionally, supplements containing DAO can be used, preferably as an addition to a low-histamine diet, not instead of it. The European Food Safety Agency (EFSA) has approved a pig-kidney extract with 0.3 mg of DAO. The available supplements should be taken 2–3 times a day, 10–15 minutes before a meal (the maximum dose of DAO is 0.9 mg per day) [25, 26].

Antihistamines that block both H1 and H2 receptors are recommended to relieve symptoms associated with the consumption of too much histamine. They are not to be taken on daily basis to combat histamine intolerance, and no clinical

trials have so far confirmed that implementation of antihistamines yields a beneficial therapeutic effect.

If life-threatening systemic symptoms occur as a result of histamine intolerance, the therapeutic procedure is analogous to anaphylaxis and involves administration of adrenaline, corticosteroids, and sufficient hydration.

If comorbidities are found, treatment of the underlying disease is of key importance, as it may also lead to HIT symptoms disappearance.

## Summary

Histamine intolerance has recently become an increasingly common problem in everyday medical practice. Its symptoms can be mild but also life-threatening. Due to the multifactorial etiology of the disease, the search for its possible causes is often difficult. As the HIT symptoms closely resemble those of an allergy, they usually result in a comprehensive diagnostic workup focused on allergies. In many patients, problems related to allergic diseases are additionally observed, which hampers the diagnosis and proper therapeutic management. For this reason, each patient in whom HIT is suspected on the basis of clinical symptoms should be carefully and individually diagnosed.

However, as HIT reactions may be triggered by a vast array of products, dietary management poses a huge challenge for the patient. The problem of histamine intolerance certainly requires further research to improve the diagnosis and therapy of this food intolerance.

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