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Summary

Histamine intolerance is a clinically heterogeneous disease. We report on a female patient who had suffered for years from weight loss, diarrhea, abdominal and headaches, flushing symptoms, and bronchial asthma, and who had been diagnosed with anorexia nervosa. Based on the course of her condition while following a low-histamine elimination diet, with continuous weight gain and improvement of all symptoms, histamine intolerance was diagnosed after considering all findings together. The condition should therefore be included in the differential diagnosis of anorexia nervosa.

Abstract

Histamine intolerance is a clinically heterogeneous disease. We present a woman who suffered from weight loss, diarrhea, abdominal pain, headache, flushing and bronchial asthma for several years. When placed on a histamine-poor diet, she experienced weight gain and improvement of other all signs and symptoms, supporting the diagnosis of histamine intolerance. Therefore, this disease should be included in the differential diagnosis of anorexia nervosa.

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Medical History

The 20-year-old, severely underweight patient reported a weight loss of 10 kg over 4 years without any change in eating habits, exercise, or use of weight-reducing medication. Extensive gastroenterological diagnostics already completed—including colonoscopy, gastroscopy, exclusion of lactose or fructose intolerance, and exclusion of sprue—had found no organic causes. From the psychiatric perspective, atypical anorexia nervosa had been diagnosed, and in 2004 the patient had been treated unsuccessfully for a total of 5 months with multiprofessional individual and group psychotherapy, psychoeducation, and supportive body, sports, occupational, and creative therapy, partly as an inpatient and later several times as an outpatient.

In the further history, the patient reported mushy stools 3 to 4 times daily, a feeling of fullness, and frequent cramping abdominal pain 30–60 minutes after meals. After drinking red wine and sparkling wine, she experienced hot flashes with marked facial flushing, nausea, and diarrhea. Gastrointestinal symptoms also occurred after eating histamine-rich foods such as tomatoes, long-ripened cheese, smoked ham, and salami. She complained of very frequent headaches with drowsiness, occasional migraine, and a strong susceptibility to infections. In addition, bronchial asthma associated with type I allergies to house dust and storage mites, cat epithelia, tree pollen, and some cross-reactive foods was known; it was treated with inhaled budesonide and formoterol twice daily and antihistamines as needed.

Clinical Findings

The patient was found to be in a markedly reduced nutritional state, with a body weight of 45 kg and a height of 172 cm (BMI 15.2, Fig. 1). Also noted were the already known scoliosis of the spine and white dermographism. The rest of the physical examination was unremarkable.

Fig. 1

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Patient with BMI 15.2 before a low-histamine diet

Diagnostics

Laboratory

A markedly elevated N-methylhistamine excretion was found in the 24-hour collected urine [14.7 µg/mmol creatinine/m^2 BSA (body surface area), reference value <6.5 µg/mmol creatinine/m^2 BSA]. Diamine oxidase activity in serum was within the normal range (12.1 U/ml, reference value >10.0 U/ml), as was serum tryptase (1.0 µg/l, normal value <13.5 µg/l). Total IgE was 456 kU/l (normal value <100 kU/l). Routine clinical chemistry parameters, blood count, and blood coagulation were normal.

Allergological Diagnostics

Based on the history, prick tests, RAST examinations, and partly provocation testing, type I allergies were diagnosed to house dust mites of the genus Dermatophagoides, storage mites, seasonal and perennial molds, cat epithelia, pollen from early- and late-flowering

trees, celery, paprika spice, thyme, coriander, caraway, anise, parsley, hazelnuts, bell pepper, apple, cherry, carrot, and tomato.

Elimination Diet

The patient followed a 3-day outpatient potato-rice diet; subsequently, during an inpatient stay, a low-histamine build-up diet including the most important food groups was introduced.

Treatment and Course

From the fifth day of the low-histamine diet, the patient had formed stools at a normal frequency for the first time in years. With a markedly improved general condition, no gastrointestinal symptoms occurred, and only one mild headache was reported. Although the patient had discontinued antihistamines and anti-asthmatic medication before inpatient admission, no asthma occurred except for one attack after provocation with thyme.

In view of this course, the medical history, and the additional examination findings, histamine intolerance was diagnosed.

The patient was informed in detail about the disease and the necessary diet. In addition, she strictly avoided the above-mentioned proven type I allergens and, after discharge, received accompanying medication with 1000 mg vitamin C, 20 mg vitamin B6, and 180 mg fexofenadine daily. Under these measures, the patient was free of symptoms, her general condition and ability to concentrate were markedly improved, and she steadily gained body weight. Five months later, the patient weighed 51 kg (BMI 17.2) and reported increased performance and well-being (Fig. 2). After dietary lapses, she reported abdominal pain, bloating, and diarrhea with weight loss. Antihistamines are currently taken only after dietary lapses to relieve symptoms. Because of the history, the elevated N-methylhistamine excretion, and this clinically decisive course, we did not perform a double-blind, placebo-controlled provocation test, which would have been burdensome for the patient.

Fig. 2

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Patient after 6 months on a low-histamine diet (BMI 17.2)

During follow-up, the patient had reached a weight of 53 kg after 16 months (BMI 17.9). The frequent infections in her prior history had not recurred.

Discussion

Histamine intolerance, which affects about 1% of the general population and mainly middle-aged women, results from an imbalance between accumulated histamine (2-[4-imidazolyl]ethylamine) and histamine degradation. While intracellular histamine is mainly broken down by histamine N-methyltransferase (HNMT), diamine oxidase (DAO) is crucial for the degradation of extracellular histamine or histamine ingested with food. Histamine degradation by DAO can be competitively inhibited by alcohol, medications, and other biogenic amines. Histamine intolerance occurs more frequently in people with atopic diseases, and histamine excess can trigger symptoms similar to allergic reactions. Elevated histamine concentrations and reduced serum DAO activity have been found in a subgroup of patients with atopic eczema and in patients with food allergy; in the former patient group, there is already evidence of a genetic basis. This has not yet been shown for other atopic diseases such as allergic bronchial asthma and allergic rhinoconjunctivitis. In inflammatory and neoplastic gastrointestinal diseases, such as Crohn's disease, ulcerative colitis, and colon adenomas, DAO polymorphisms have been found, which may also suggest a genetic predisposition.

The clinical symptoms of histamine intolerance vary widely and, unlike an IgE-mediated allergic disease, are dose-dependent.

When the individual histamine tolerance threshold is exceeded, affected individuals may experience nausea, abdominal pain, meteorism, diarrhea, headaches, runny nose, nasal obstruction, asthma attacks, urticaria, itching, flushing symptoms, dysmenorrhea, hypotension, tachycardia, and arrhythmias, among other symptoms. Weight loss may also occur secondarily as a result of gastrointestinal symptoms.

A diagnosis of histamine intolerance becomes likely when at least two of the listed symptoms occur and improve with a low-histamine diet and antihistamines. In addition to allergological diagnostics, mastocytosis and other diseases, such as gastrointestinal disorders, should be excluded. In cases of weight loss, eating disorders—especially prevalent among girls and young women, such as anorexia nervosa and bulimia—as well as organic causes of weight loss should also be ruled out. Usually, elevated concentrations of histamine or its metabolite N-methylhistamine and/or reduced serum DAO activity can be demonstrated; alternatively, a double-blind, placebo-controlled histamine provocation test can establish the diagnosis.

Treatment is based on a low-histamine diet with avoidance of alcohol, especially red wine, and fermented or microbially produced foods that are rich in histamine or release histamine, such as aged cheese, smoked foods, chocolate, tomatoes, and citrus fruits. The additional use of an effective antihistamine as needed is useful. Accompanying medication with vitamins B6 and C as DAO cofactors may also be attempted. Histamine-releasing or DAO-inhibiting medications, such as acetylsalicylic acid, metamizole, metoclopramide, clavulanic acid, and prilocaine, should be avoided. Additional oral administration of DAO in capsules showed symptom relief in observational studies; however, controlled studies are still lacking.

This relatively simple treatment can lead to complete freedom from symptoms and a marked improvement in quality of life.

Differential Diagnosis

The weight loss and other symptoms could, in terms of differential diagnosis, be an expression of:

- a gastrointestinal disease, such as sprue, lactose or fructose intolerance, ulcerative colitis, or Crohn’s disease;
- an eating disorder, such as anorexia nervosa;
- a food intolerance or allergy; or
- occult mastocytosis.

Practical Conclusion

In summary, this case shows that in patients suspected of having anorexia nervosa, clinically heterogeneous and often unrecognized histamine intolerance should also be included in the differential diagnostic considerations. A low-histamine diet can relieve symptoms up to complete freedom from symptoms and can decisively improve quality of life.

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Conflict of Interest

The corresponding author states that there is no conflict of interest.

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