CASE REPORT

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Histamine intolerance caused by Diamine Oxidase (DAO) deficiency – case report

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Abstract

Histamine is a biogenic amine, which occurs naturally in the human body. Histamine can be metabolised with Diamine Oxidase (DAO) Enzyme. It is estimated that in 1% of people, as a result of an imbalance between the supply and degradation of histamine, a condition called histamine intolerance (HIT) develops. The case report describes a 40-year-old women who visited the Emergency Room several times due to quickly increasing face oedema, rush, chest pain and dyspnoea after eating meals containing histamine. For many years, the patient has struggled with non-specific symptoms. The woman decided to have a test performed to determine the enzymatic activity of DAO in the blood serum. The result was 5 U/ml, which indicates a significant shortage of DAO. Taking into consideration the symptoms the patient presented, extensive differential diagnosis, which excluded the presence of other diseases and serum DAO activity test, it was possible to diagnose histamine intolerance caused by DAO deficiency.

Key words

histamine intolerance, biogenic amine, diamine oxidase deficiency

INTRODUCTION

Histamine (2- [4-imidazolyl] ethylamine) is a biogenic amine, a derivative of imidazole, that occurs naturally in the human body. The name originates from the Greek word *histios* – tissue, which indicates the presence of histamine in many tissues, especially in the lungs, skin, nasal mucosa and stomach. It was isolated in 1910 from *Claviceps purpurea* by British pharmacologist Sir Henry Dale [1], a Nobel laureate who was also the author of the histamine theory of allergic diseases, revealing one of the key functions of this amine in human pathophysiology. The endogenous source of this substance is the histidine decarboxylation reaction with the participation of pyridoxal phosphate, the active form of vitamin B6 [2]. It mainly occurs in mast cells, basophils, platelets, histaminergic neurons, and enterochromaffin cells (EC) of the gastrointestinal tract. The synthesis of histamine is stimulated by peptides (substance P), elements of the complement system (C3a, C5a), cytokines (PAF, IL-1, IL-3, IL-8, GM-CSF), adenosine, lipoproteins, hyperosmolarity or hypoxia [1, 2]. External sources of histamine are foods rich in histamines (e.g. tomatoes, spinach, meat, eggs, fish, citrus fruits and dairy products) and bacteria capable of carrying out the histidine decarboxylation reaction – representatives of the genus *Lactobacillus*, *Pediococcus*, *Photobacterium* or *Klebsiella* [1]. By affecting the histamine receptors H1 and H2, this substance causes smooth muscles spasm, dilation and increased permeability of blood vessels, increased mucus secretion, tachycardia, arrhythmias, hypotension and increased gastric acid secretion [2]. Through H3 receptors present in the hypothalamus and the central nervous system, it acts as a neurotransmitter and participates in the regulation of the sleep-wake rhythm [1]. H4 receptors are also present in the body, the role of which is still being researched.

Histamine can be metabolized by oxidative deamination by diamine oxidase (DAO, previously named histaminase) and methylation of the imidazole ring with the participation of histamine-N-methyltranferase (HNMT), depending on the location of the amine in the body [1, 2]. Due to the stimulated secretion of DAO by epithelial cells previously storing the amine, its role in the transformation of exogenous histamine, and the intracellular HNMT enzyme – endogenous histamine [2]. Despite the greater affinity of HNMT for the product, it is DAO that is assigned a key role in the degradation of histamine [3]. DAO activity varies depending on its location in the body – the greatest in the small intestine, ascending colon, placenta and kidneys [2], and requires the presence of vitamins B6, C and copper to function properly [1]. HNMT, on the other hand, plays a key role in the degradation of histamine in the bronchial epithelium, and is also highly active in the liver and kidneys with ubiquitous production [2].

As a result of the imbalance between the supply and degradation of histamine, a condition known as histamine intolerance (HIT-histamine intolerance) [2, 3]. Histamine-rich foods may also become intoxicated as a result of excessive consumption of histamine-rich foods [4]. A case of histamine intoxication was first described over 60 years ago, caused by the consumption of mackerel from the *Scombridae* family (hence the other name of intoxication – scombroidosis), initially associated with food poisoning [5]. The above-mentioned balance may also be disturbed by deficiencies in

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histamine metabolizing enzymes, mainly DAO. This results in increased amine uptake, while its degradation is impaired, which leads to the achievement of high plasma concentrations. Enzymatic dysfunction may be caused by acquired blockage of DAO and HNMT (drugs, alcohol, intestinal diseases) or a congenital reduction in their synthesis [3]. As a result of increased levels of histamine (> 1.0 ng/ml), numerous clinical symptoms develop, such as urticaria, itching of the skin, gastrointestinal disorders, sneezing, rhinitis, headache, arrhythmia and hypotonia [2–4]. Histamine intolerance develops mainly in middle-aged women [1]. It affects up to 1% of the population, and due to the wide spectrum of symptoms, it is often not included in the differential diagnosis.

During last decade researchers worldwide have described the effects of enzyme deficiencies in the histamine pathway. The aim of this study is to analyze a clinical case of histamine intolerance due to DAO deficiency which, in combination with the results of available descriptions and studies, will allow conclusions to be drawn regarding the diagnosis, course and treatment of this disease entity.

CASE REPORT

A 40-year-old female patient with the result of the DAO deficiency test obtained on the 1 December 2021, reported to the Nutritional Treatment Clinic at Independent Public Teaching Hospital No 4 in Lublin, P:oland (February 2022), where she was referred by a dietitian due to significant weight loss caused by the use of a restrictive elimination diet since 4 December 2021. Currently, the patient weighs 42.5 kilograms with a height of 168 centimeters. BMI for such parameters is 14.88 kg/m^2 and indicates severe thinness. Anorexia was ruled out in the patient during the psychiatric consultation. Attempts at feeding with nutritional supplements and dietary advice did not bring the desired results. In the Nutritional Treatment Clinic, the patient was offered parenteral treatment.

In the interview, the patient reported symptoms of DAO deficiency many years before the diagnosis. Since childhood, the patient has been constantly accompanied by swelling of the nasal mucosa, with intensification after meals since 2000, nasal congestion when the temperature changes from colder to warmer, when staying in new rooms, regardless of the season; therefore, she has been using Otrivin (xylometazoline) for several years. Since 1996, she has had dermatological consultations due to recurrent itchy hives with purulent pustules on the face and back, and dry skin despite the therapy. As a treatment, Amoksiklav (amoxicillin with clavulanic acid) was used orally, topically on the face with hydrocortisone and boric acid. Often paroxysmal, lasting about 2 hours, spontaneously resolving nausea, pressure drops to 80/40 mmHg, tachycardia, increase in body temperature not exceeding 37.5°C, severe headache, burning eyes, swelling and rash on the face, weakness, feeling of fullness, flatulence and epigastric pain, which the patient associates with eating food, e.g. tomato sauce, or after using a hair dye.

In 2005, she visited a doctor because of palpitations, but further diagnostics ruled out a cardiological disease. In 2012, neurosis was excluded from the patient. In 2020, the patient was diagnosed with anaemia based on test results: iron (Fe) 25 mg, HGB 10 g/dl, ferritin 2 mg. Celiac disease and lactase deficiency were excluded. Vitamin D3 deficiency was found, the level of which was 13 ng/ml.

The patient was operated on three times due to scoliosis of the thoracic and lumbar spine. Since the operation in 2011, the patient experienced depression and anxiety disorders, and felt 'tightness in the abdomen', strong tension, fear of further weight loss because after the surgery her weight dropped from 51 kg to 46 kg, heart palpitations, generalized anxiety and anxiety attacks. Initially, Lerivon (mianserin) 30 mg (2011) was included in the therapy, then, as a result of unsatisfactory therapy, Doxepin (doxepin) 90 mg and cognitive-behavioural therapy with satisfactory results. Since menarche, the patient reported severe abdominal pain, inconvenient vomiting, diarrhea, tingling in the legs accompanying menstruation, which decreased only around the age of 30. The patient has no children.

Starting from 2019, after eating certain meals, such as tomato sauce, rye flour pancakes, carrots fried with millet flour, potatoes with turkey, the patient repeatedly reported to the Emergency Room due to the development of allergic symptoms: rapidly increasing swelling and rash on the face (Fig. 1), burning, shortness of breath in the chest, feeling of fullness in the stomach, weakness, tachycardia, flatulence, for which hydroxyzine and a Proton Pump Inhibitor (PPI) were used. The patient arbitrarily decided to take Clatra (bilastine) 80 mg and Lirra Gem (levocetirizine) 5 mg orally. On 4 December 2021, after taking a bath, the patient developed a rash on her hands, dyspnoea (SpO_2 = 75%). Before visiting the hospital, the patient took Zyx (levocetirizine), 2 hours later the saturation reached 90%, the rash resolved in the emergency department, and pulmonary embolism was excluded. These events prompted the patient to perform

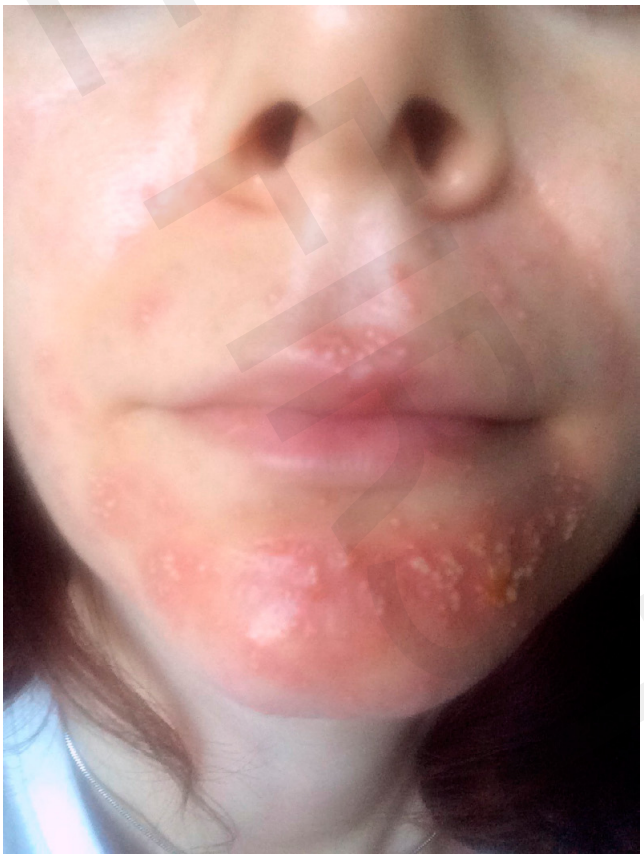

Figure 1. Erythema and rash after the patient ate tomato sauce

a commercial test to determine the enzymatic activity of DAO in the blood serum. The result was 5 U/ml, which indicates a significant deficiency of DAO, because according to the laboratory conducting the determination, the reference values of its normal activity are higher than 10 U/ml. From 4 December 2021, the patient remains on a diet excluding products containing histamine.

In October, the patient fell ill with COVID-19. The patient was not vaccinated against COVID-19, the infection was mild (body temperature 37.5°C, weakness, tachycardia). The patient reported discomfort after eating food and was taking Sanprobi Stress probiotics. After the disease, laboratory tests detected an increase in D-Dimers to the level of 1017μg/l. Treatment with heparin (Neoparin) and levocetirizine 5 mg orally was started, after discontinuation of D-Dimer at the level of 1,300μg/l.

On 29 December 2021, after a visit to a dietitian and a hydrogen-methane test on 7 January 2022, the patient was diagnosed with SIBO – hydrogen and methane growth of the intestinal flora; pharmacotherapy was started: Neomycin 2x250 mg and Xifaxan (rifaximin) 3x400 mg. A panel of allergological tests performed (300 antigens) showed allergy only to shrimp. Mastocytosis, parasitic infection, Mast Cell Activation Syndrome (MCAS) and mycosis were excluded. In turn, the gastroscopy performed 3 times (2012 and twice in 2020) showed no pathology. Family history of type 2 diabetes and maternal hypertension, but no disease burden in other family members.

DISCUSSION

The above-description of the patient perfectly presents the wide spectrum of symptoms that people with histamine intolerance may present. Due to non-specific ailments and their multiplicity of occurrence, it is often difficult to make a correct diagnosis. This is what happened in the patient described this case report, who had been unsuccessfully treated for many years. The turning point turned out to be the intensification of the reported ailments, forcing the patient to seek help in the conditions of the Hospital Emergency Departments when the symptoms resembled a life-threatening condition. It is worth noting that the patient decided herself to perform a serum diamine oxidase test, the result of which, after taking into account the performed differential diagnosis, allows with a high probability to make a diagnosis of histamine intolerance due to DAO deficiency. Unfortunately, the test performed by the patient cannot be considered the gold standard in diagnostics due to the variable level of DAO in the serum [6]. The performed test enables the quantitative evaluation of DAO in serum thanks to the use of the ELISA method, which involves 2 polyclonal antibodies directed against recombinant DAO. In the first step, blood samples are added to the wells of a microplate containing a polyclonal rabbit anti-DAO antibody. The enzyme binds to the antibody. A biotinylated anti-DAO polyclonal antibody is then added to each well, followed by the addition of a streptavidin peroxidase conjugate to produce a so-called 'sandwich' consisting of the first DAO antibody – biotinylated antibody – streptavidin peroxidase conjugate. The colour changes when a peroxidase substrate is used and an acid is added to complete the reaction [7]. The colour change obtained enables assessment of the DAO concentration in the serum [8]. Despite the controversy regarding the possibility of making a diagnosis based on the above-mentioned test, some authors suggest that these tests may be helpful in identifying people with histamine intolerance, including in the case of suspected genetic background, which is likely in the case of the patient described [5]. Taking into account the fact that the symptoms had been experienced by the patient since school years, it is possible to suspect a congenital basis of DAO deficiency, which may be due to genetic factors [5]. This hypothesis may be contradicted by an insignificant family history. One of the abnormalities in the patient's tests was the presence of SIBO (small intestine bacterial overgrowth). This fact may also indicate the diagnosis of histamine intolerance in a patient, due to emerging reports of changes in the intestinal microflora in patients with histamine intolerance [9]. The first symptoms related to histamine intolerance occurred before the patient began taking the drugs, while in the period immediately preceding the exacerbation of symptoms, the patient did not use them either, which basically excludes drug-induced histamine intolerance.

The basic treatment of histamine intolerance caused by DAO is the use of a diet based on products with a low histamine content. It has been shown to be effective in reducing symptoms and increasing the DAO level after about 2 months of dieting [10]. This diet is used by the patient described, but due to the initial exclusion of many foods due to malaise, it resulted in malnutrition. Unfortunately, the formulation of a histamine-free or low-histamine diet is often difficult, due to the often varied content of this amine in the same products [11], as well as discrepancies in the literature [5]. Fish, seafood, some vegetables, such as spinach, tomatoes, fermented meat products and cheese, can undeniably be considered histamine-rich foods [12]. Currently, the patient has expanded the products to include quinoa, porridge, some vegetables, melon and blueberry, and also consumes highly nutritious preparations used in nutritional treatment. From the moment of visiting the Nutritional Treatment Clinic, the patient gained 2 kilograms, reporting an improvement in well-being. Another method of treatment is taking DAO supplements to break down histamine in the meals consumed [1] which the patient is also using.

The undoubted advantage of the described method of treatment is the possibility of maintaining a less restrictive diet. The studies conducted so far have confirmed the effectiveness of the use of DAO supplements, and have resulted in the reduction in the severity of at least one symptom in 93% of respondents [5]. Antihistamines have been shown to have no effect on DAO activity [12], and therefore should only be used as a symptomatic and short-term treatment.

CONCLUSIONS

The symptoms presented by the female patient described clearly suggested the presence of histamine intolerance. This is evidenced by their intensification, especially after consuming products containing a large amount of this biogenic amine. The patient underwent extensive differential diagnosis which ruled-out the presence of other diseases, including anorexia, celiac disease, neurosis, lactose deficiency, myocardial infarction and pulmonary embolism, which also supported the presence of a diagnosis The test performed by the patient

to assess DAO activity in the blood serum, which showed its deficiency, was also important. Despite the controversy regarding the usefulness of the mentioned test in diagnostics, many sources consider it extremely useful in the diagnosis of histamine intolerance caused by DAO deficiency. Due to the above, taking into consideration the clinical manifestations, the exclusion of other diseases and the improvement of well-being after the use of a histamine-free diet, this supports the diagnosis of histamine intolerance caused by DAO deficiency.

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