ALLERGY TO HYPOALLERGENIC METALS

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Every year the number of people with allergic diseases significantly increases worldwide. It might be explained by many factors, e.g., environmental pollution, nutrition and food quality, uncontrollable use of medications, quality of home cleaning or use of excessive amount of chemicals. The main food allergens are cow's milk, eggs, soybeans, peanuts, seafood and fish. Severe allergic reactions may be drug induced, most commonly by antibiotics, ACE inhibitors, and non-steroidal anti-inflammatory drugs. Some substances, which until recently were considered hypoallergenic, are reported to cause hypersensitivity with increasing incidence. These include some metals, such as titanium, cobalt, chromium and others. Titanium is widely used in orthopaedics, traumatology, dentistry, and other branches of medicine because it is highly resistive to corrosion, hypoallergenic, inert, and non-toxic to the human body. Unfortunately, the diagnosis of metal allergy is not widely available today. Since not all allergic reactions mediated by IgE-dependent mechanism, serological diagnosis becomes impossible. The diagnostic option in such cases are patch tests with possible culprit allergens.

Key words: allergy, metal, angioedema

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INTRODUCTION

Allergy is a disease of the 21st century. According to the results of studies conducted in Europe, from 10 to 40% of the population have some manifestations of allergy. Due to urbanization, the prevalence of allergic diseases is 4-6 times higher among the urban population, than among rural. For the period from 2005 to 2015, the number of patients who sought medical help due to allergy increased 7-fold. Atopic dermatitis, allergic rhinitis, and asthma are often diagnosed in children, whereas allergic rhinitis and bronchial asthma are most common among adults. About 5% of the US population had a history of anaphylaxis (1). Up to 20% of patients in Europe live with the threat of possible attacks of asthma, anaphylactic shock, or even death from an allergic reaction.

The most dangerous allergic reactions are anaphylactic shock and angioedema, which often develop after food intake or parenteral use of medications. The most common dietary allergens are nuts, fish, seafood, cow's milk and eggs (2). The greatest risk of anaphylactic reaction pose the following drugs: antibiotics, non-steroidal anti-inflammatory agents, anaesthetics, radiocontrast media, serum and blood components, ACE inhibitors, anticonvulsants, neuromuscular blocking agents, recombinant proteins and monoclonal antibodies, platinum, and narcotics (3).

Specific attention should be paid to the group of hypoallergenic substances, which were thought not to cause allergic reactions. This includes some metals, such as titanium, cobalt, chromium that are widely used in medicine. However, today there is growing body of evidence that they may cause allergic reactions.

CLINICAL CASE

A 39-year-old patient without harmful habits came to an allergist complaining of swelling of the tongue, lips, eyelids, which cannot be associated with taking of certain medications or food. The patient gave a permission to publish his personal data and test results.

THE RESULTS OF PHYSICAL EXAMINATION

The upper and lower lips were swollen and enlarged in size along with a noticeable oedema of the right eyelid; skin was clean and moderately wet. Nasal breathing was laboured due to oedema of mucous membrane. A tongue of normal size, covered with a white furring. Lung auscultation revealed vesicular breathing without wheezes. Heart sounds were clear and regular with no audible murmurs. The abdomen was soft and non-tender to palpation; the tenderness was revealed in the Kehr's point (the intersection of the outer edge of the right rectus abdominis muscle and costal arch, corresponding to gallbladder projection on the anterior abdominal wall).

HISTORY OF THE DISEASE

Symptoms of angioedema (facial swelling, sometimes oedema of toes) were present for the past 18 months. Initially he was treated himself taking oral antihistamines (levocetirizine, cetirizine) and even dexamethasone parenterally (1-2 ml). Symptoms had disappeared for a few weeks, but subsequently appeared again. Their occurrence the patient could not associate with the use of certain food or drugs. There were no symptoms of allergy before, as well as allergic diseases among family members and first-degree relatives. The patient was previously healthy, denied trauma or major surgery. About two years ago, he underwent a tooth implantation.

After appearance of tongue swelling and difficult breathing, he sought medical help and was referred to an allergist. After 48 hours of treatment with Clemastine Fumarate (Tavegyl) and Dexamethasone intravenously the swelling and breathing difficulties disappeared, lung auscultation revealed vesicular breathing. Five days after hospital discharge and discontinuation of medications the recurrence of upper lip oedema appeared after the consumption of soup prepared with frozen seafood. The patient was re-admitted to the hospital for further diagnostics.

THE RESULTS OF ADDITIONAL TESTS

Complete blood count, blood biochemistry (table 1) and urinalysis showed no abnormalities. The Wassermann test, test for HIV infection and PCR for of hepatitis B, C, and D viruses were negative. To exclude systemic diseases, including vasculitides, blood serologic testing for the main markers of these diseases (i.e., Jo-1, Scl-70, Sm, RNA, SS-A 52/60, SS-B, chromatin, ribosomal protein, biphasic DNA, antinuclear antibody, Sm/RNP) were performed with negative results.

Table 1.
The results of complete blood count and blood biochemistry

Parameter, units	Patient's value	Reference ranges
Haemoglobin, g/dl	15.2	14-18
RBC count $x10^{12}$/l	4.2	3.5-5.4
MCH pg per cell	28.6	27-31
Reticulocytes, %	1	0.5-1.5
WBC count, $x10^9$/l	5.6	4.0-10.0
Differentials, %		
Neutrophils	66	60-70
Lymphocytes	22	20-45
Monocytes	5	4-8
Basophils	1	0-1
Eosinophils	5	2-4
Platelet count, $x10^9$/l	210	150-300
ESR, mm/hour	9	3-15
Total bilirubin, µmol/l	18	5.1-20.5
ALT, IU/l	26	0-40
GGT, IU/l	22	0-35
Alkaline phosphatase, IU/l	265	0-270
Total protein, g/l	63	60-80
Glucose, mmol/l	5.1	3.9-5.5
Total cholesterol, mmol/l	3.4	3.0-4.9
Blood urea, mmol/l	4.9	2.5-6.7
Creatinine, µmol/l	82	53-115
Total Ig E, IU/ml	110	0-110

Upper gastrointestinal endoscopy revealed erosive gastropathy, duodeno-gastric and gastro-esophageal reflux. Elevated levels of IgG against *Helicobacter pylori* (6.26 units/ml, upper reference range of 0.9 units/ml) were detected. A 10-day eradication therapy had been performed (amoxicillin 2000 mg/day, clarithromycin 500 mg/day, omeprazole 20 mg/day, domperidone 20 mg/day).

The abdominal and thyroid gland ultrasonography (USG) showed normal size, structure and echogenicity of the liver; enlarged size of the gallbladder (100 x 26 mm) with the wall thickening up to 6 mm, gallbladder's neck bend and biliary sludge. The thyroid gland was not enlarged, homogeneous with normal structure without nodes or tumors.

A bacteriological stool test revealed enteropathogenic flora with no Bifidobacteria and Lactobacteria and slightly increased number of Candida. Phage therapy did not give any clinical effect.

ALLERGIC TESTING

A prick test with the most common allergens *(table 2) was performed 14 days after* discontinuation of antihistamines*, followed by* the determination of the causative allergens by *molecular diagnostics (table 3).*

Table 2.
The results of patient's skin prick test

Allergen	Result	Allergen	Result
Histamine	6x6 cm	Dander & epithelia, meet	
Control	2x2 cm	*Felis domesticus*	n
Pollen of herbs, weeds and trees		*Canis familiaris*	n
Amaranthus retroflexus	n	*Equus caballus*	n
Artemisia vulgaris	n	*Bos domesticus*	n
Phleum pratense	n	*Sus domesticus*	n
Urtica dioica	n	*Oryctolagus* spp.	n
Betula verrucosa	n	*Meleagris gallopavo*	n
Fraxinus excelsior	n	*Cereals and seeds*	
Quercus robur	n	*Avena sativa*	n
Moulds & Yeasts		*Hordeum vulgare*	n
Alternaria alternata	2x2 cm	*Fagopyrum esculentum*	n
Aspergillus fumigatus	2x2 cm	*Oryza sativa*	n
Penicillium chrysogenum	n	*Triticum aestivum*	n
House dust mites		Vegetables	
Dermatophagoides farinae	3x3 cm	*Allium sativum*	n
Dermatophagoides pteronissinus	3x3 cm	*Daucus carota*	n
Fruits		*Solanum tuberosum*	n
I	n	Others	
Fragaria ananassa	n	*Cyprinus carpio*	n
Malus domestica	n	*Glycine max*	n
Vitis vinifera	n	Juglans regia	n

n = negative result

Table 3.
The results of molecular allergic testing

Parameter, units	Patient's value	Reference ranges
sIgE, IU/ml	142	<100
d1 (*Dermatophagoides pteronyssinus*), kU/L	0.41	<0.35
rDer p10 (Tropomyosin), kU/L	0.34	<0.35
rDer p1 (Cysteine Protease), kU/L	<0.1	<0.35
rDer p2 (NPC2 Family), kU/L	<0.1	<0.35
Dermatophagoides farinae		
rDer f1 (Cysteine Protease), kU/L	0.22	<0.35
rDer f2 (NPC2 Family), kU/L	0.13	<0.35
sIgE *Aspergillus fumigatus*, kU/L	0.01	<0.1
sIgE *Aspergillus niger*, kU/L	0.01	<0.1
sIgE *Penicillium chrysogenum*, kU/L	0.01	<0.1

Modern diagnostic methods may identify more major and minor allergens, but after receiving the results of allergic testing and taking into consideration that the patient had no clear clinical signs of household allergy, it was decided not to perform further detection of molecular allergens. In addition, allergen-specific immunotherapy (ASIT) was not indicated in this case. In order to prevent cross-reactions, the patient was recommended to limit the use of seafood with chitin shell.

Worms and parasites are other possible causes of angioedema and urticaria (4,5). Patient's blood serology revealed IgG type antibodies against *Toxocara canis* of 1.3 S/CO. Initiated course of albendazole therapy (400 mg daily) was poorly tolerated by the patient. After appearance of tongue and upper lip swelling with itching of the skin the treatment was stopped ahead of schedule.

During the recent years, more and more reports had emerged about the effect of the gut microbiota on the immune system and the course of allergic diseases (6-8). Moreover, the «leaky gut», i.e. the state of impaired barrier function of the intestine might lead to penetration of intestinal flora into the bloodstream, causing activation of the immune system, inflammatory state and cholestasis (9). These finding are consistent with patient's clinical signs, symptoms, and results of abdominal USG and stool tests. The following therapy had been prescribed for one month: ursodeoxycholic acid 500 mg daily + polymethylsiloxane polyhydrate (Enterosgel) + Lactobacillus rhamnosus GG in combination with his usual dose of desloratadine. During the course symptoms were absent, but they appeared again shortly after discontinuation.

Thereafter, the patient was consulted by an otolaryngologist to exclude chronic infections of the upper respiratory tract. After negative results, a detailed history was taken again. Attention was paid to the fact that symptoms appeared a month after the insertion of a dental implant. Today, the most commonly used method for detecting allergies to metals is a patch test. The patient was consulted by an allergist at a private medical clinic in Norway, where sensitization to house dust mites was confirmed as well as increased sensitivity toward chromium and cobalt was detected. ASIT was not recommended. Besides, the levels of C1-esterase inhibitor (C1-INH) protein and C3 and C4 components were measured, and their normal results excluded hereditary angioedema.

Finally, it was decided to remove the dental implant. To date, 6 months after removal of the implant, the general condition of the patient significantly improved. There were no episodes of difficulty breathing

or swelling of the tongue; a few cases of lip oedema easily relieved by levocetirizine. During this period, the patient did not follow any elimination diet.

DISCUSSION

What could provoke the development of angioedema in this patient? Perhaps, the dental implant has launched a cascade of allergic reactions. A literature research for similar clinical cases revealed that after the tooth implantation allergic reactions might occur not only toward titanium, but also to other materials used in implant composition, e.g., nickel, palladium, chromium and cobalt. Metal ions and particles are released into the surrounding tissue over time (10,11) Although titanium is considered to be a hypoallergenic biocompatible metal with a very good osseointegration and high resistance to corrosion that makes it widely usable in orthopaedics, dentistry and other branches of medicine, allergy to it also develops (12,13). Persistent inflammation due to metal implant may cause variety of symptoms, e.g., muscle spasms, myofascial pain, headaches, tinnitus, vertigo, and angioedema. A chronic inflammation due to prolonged exposure can lead to loss of bone strength, osteolysis and fractures (14).

Even after removal of metal components, the symptoms of allergy sometimes remain (11). Why? Firstly, produced antibodies circulate in the blood during a long period and can cause repeated oedema, even after the elimination of the culprit allergen. Secondly, allergy to metals maybe related to other than IgE-associated mechanisms. Due to oxidation, metal ions released from the alloy of implant. They are potent haptens that penetrate the skin or mucous membranes and activate epithelial cells that produce various pro-inflammatory cytokines or chemokines. Later, activation and migration of haptenated protein-loaded antigen presenting cells (macrophages, dendritic cells) to the draining lymph nodes occurs. This, in turn, causes proliferation, activation and differentiation of hapten-specific T cells, which later migrate out of the lymph nodes. Further re-exposure to the same hapten leads to their activation and entering to the bloodstream that cause visible signs of hypersensitivity within 48-72 hours after exposure (15).

Finally, metal exposure may occur not only from implanted orthopedic devices, but also from other sources. Thus, metals alternatively enter the human body and can cause allergic reactions. For instance, titanium is a part of sunscreens, confectionery (colored decorations) and chewing gums, toothpastes and coating of medicines (16). Cobalt is used in the production of metal alloys and blue or green pigments that is why sensitization may occur due to the use of costume jewellery or tattoo. Besides, it is a component of detergents and cosmetics, as well as fertilizers, which improve the growth of plants (17). Chromium protects metals from corrosion, and wood from fungi and termites; it is also used in leather tanning, for manufacturing of dyes, paints, detergents, cosmetics, copy machine toner, cement and some alloys, particularly stainless steel [18]. Food contamination with these metals is also possible because they are used for preservation of vegetables, fruits, fish and meat (19). Therefore, the use of such products may also contribute to exacerbation of allergy.

Interestingly, that both cobalt and chromium are useful microelements. Cobalt is a core element of vitamin B_{12} that is necessary for DNA and myelin synthesis. Besides, it is necessary for the formation of some neuronal proteins, amino acids and neurotransmitters. Cobalt salts are used for therapy of some types of anaemia and in sport alternatively to blood doping (20). However, inorganic ion Co forms are toxic, and the longer they are stored in the body, the more pronounced cellular changes they cause. Cobalt enters the body with food, via inhalation and through the skin (20). Long-term exposure to cobalt may cause cardiomyopathy, lung and neurological damage (21).

Chromium nutritional bioavailability and toxicity is mainly determined by its oxidation state, i.e., trivalent Cr is essential microelement, whereas hexavalent Cr is known occupational hazard, mutagen and carcinogen (22). As a microelement, chromium takes part in the metabolism of carbohydrates, lipids, and proteins mainly by increasing of insulin efficacy and glucose utilization by muscles thereby improving insulin sensitivity (23). It also reduces the serum leptin concentration (24). Although certain mechanisms of action are not clearly understood, chromium may be involved in increasing number of insulin receptors, their activation in the presence of insulin and binding to it. It was also shown that chromium supplement in postmenopausal women decreases excretion of calcium with urine that may be beneficial for prophylaxis of osteoporosis (25). Chromium contains many foods such as soybeans, corn, oatmeal, broccoli, mushrooms, potatoes, spinach, bananas, carrots, blueberries, liver, processed meats, chicken, beef, egg yolks, molasses, cheese, grape juice and honey; there are also many dietary supplements, but their beneficial effect on the human body are under investigations (26).

CONCLUSION

Angioedema is one of the most serious allergic reactions that significantly worsen quality of life and may be life threatening. To elucidate the etiology careful history taking with attention to all complaints and their appearance as well as precise further investigations are required. Substances that were considered hypoallergenic, i.e., titanium, cobalt, chromium, may cause allergic reactions. Allergy to metals is particularly difficult to diagnose and treat.

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SAŽETAK

ALERGIJA NA HIPOALERGENE METALE

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Svake se godine u svijetu značajno povećava broj ljudi s alergijskim bolestima. To se može tumačiti mnogim faktorima kao što su onečišćenje okoline, kakvoća hrane i prehrane, nekontrolirana upotreba lijekova, kvaliteta kućnog čišćenja ili prekomjerno korištenje kemijskih tvari. Glavni alergeni hrane su kravlje mlijeko, jaja, soja, kikiriki, morski rakovi, školjke i ribe. Teške alergijske reakcije mogu uzrokovati lijekovi, pretežno antibiotici, inhibitori ACE i nesteroidni protuupalni lijekovi. O nekim se tvarima za koje se donedavno smatralo da su hipoalergene izvještava da mogu uzrokovati preosjetljivost sve veće incidencije. To uključuje neke metale kao što su titan, kobalt, krom i ostali. Titan se naveliko upotrebljava u ortopediji, traumatologiji, zubarstvu i drugim granama medicine jer je jako otporan na koroziju, hipoalergičan, inertan i za čovjeka neotrovan. Nažalost, dijagnoza alergije na metale ne može se naširoko utvrditi. Kako nisu sve alergijske reakcije posredovane mehanizmom ovisnim o IgE, serološku dijagnostiku nije moguće utvrditi. U takvim su slučajevima dijagnostičke opcije testovi krpicom *(patch tests)* s mogućim uzročnim alergenima.

Ključne riječi: **alergija, metal, angioedem**