

IS FOOD ALLERGY A CIVILIZATION-RELATED DISEASE?

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ABSTRACT

Introduction. Civilization-related diseases are defined as diseases encompassing a global range, whose appearance or spreading issues have been largely caused as a result of the advances of modern civilization. Thus, such diseases are also interchangeably termed diseases of the 21st century. Allergy, i.e., an organism's abnormal immune reaction to exposure to an allergen, due to its increasing incidence, especially in developing countries, is occasionally called "an epidemic of the 21st century". Issues concerning food allergy are significant ones with respect to allergies as such.

Aim. This work aimed at reviewing the most current literature concerning food allergy.

Discussion. The incidence of adverse reactions to food varies. Reaction depends on the allergen type, patient's age, type of evaluated mechanism, and local diet. Potentially, each food may cause sensitivity; however, in order for a reaction to occur several conditions must be fulfilled. Allergens are mainly water-soluble glycoproteins ranging in size from 10 kDa to 70 kDa. Cases of allergies caused by smaller particles (approx. 3 kDa) or larger ones (up to 100 kDa) are also known. The increased prevalence of food allergies results from an unfavorable combination of genetic and environmental factors.

Conclusions. The incidence of food allergies is on the increase. The symptoms are intensified and regress at more advanced ages, whereas diagnostic and treatment complexities place these diseases among civilization-related diseases of the present century.

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INTRODUCTION

The phenomenon of food allergy is not new. Reports of ancient historians describing the various reactions of people to food consumed are known. However, only those advances which took place in science within the last century, exhibited the full scale of this phenomenon. The term "allergy" was introduced in 1906 by an Austrian physician Clemens Johannes von Pirquet, who was a pediatrician and professor at Universities in Wroclaw and Vienna. This term derives from the Greek *allos* – different and *ergos* – reaction. Reaction results from exposure to antigen (allergen). It is estimated that allergies are the 5th most frequently occurring diseases. The more frequent medical conditions are cancers, cardio-vascular diseases, pulmonary diseases, and AIDS [10, 19, 21].

Allergy is the abnormal reaction of an immune system that has been activated by exposure to an allergen which a given organism is sensitive to. At first contact with an allergen, the immune system of a person prone to allergies produces specific antibodies; an allergic reaction occurs only as a result of further exposure to the given allergen. Allergy is thus a specific immune response which does not occur in healthy people; whereas food allergy is an abnormal immune response leading to various, repeated clinical symptoms. These symptoms occur after having consumed food to which a given person is sensitive. In this era of technological advances and the globalization process, eating habits undergo changes in each geographical location worldwide. Vegetables, fruit, herbs, previously considered to be scarce, are currently rather commonly served throughout the world. The fact that the alimentary system is quite complex and extensive also contributes to the increase of food allergy incidence. It is estimated that the surface area of the mucous membrane of the alimentary tract amounts approximately to 300 m², which makes it the largest zone of interactions with environmental factors within the organism.

MATERIALS AND METHODS

Available literature on the subject has been collected and grouped thematically. Describing allergy from the perspective of a civilization-related disease has been attempted.

AIM

This work aimed at reviewing the latest literature concerning food allergy in order to characterize this disease entity, as well as to point out those dangers which may arise as a result of developments in civilization.

DISCUSSION

Food allergy is one of the undesirable reactions which appear as a result of food consumption. Undesirable reactions to foods can be divided into toxic and non-toxic ones. The non-toxic reactions are further subdivided into food allergy and food intolerance related to non-immune mechanisms, including, e.g., congenital and acquired enzyme deficiencies within the alimentary tract. Food allergy refers to clinical symptoms caused by pathogenic immune mechanisms. Peyer's patches, located in the lymphoid tissue of the alimentary tract, are directly responsible for the allergic reaction. Exposure to an allergen leads to a disturbance in the Th (CD4) to Tc/Tc (CD8) lymphocytes ratio and IgE-mediated allergic reactions.

An allergic reaction is directly caused by substances released by mastocytes and basophils (among others, serotonin and histamine) and cytokines. Peyer's patches, located in gut associated lymphoid tissue (GALT) are constantly stimulated by antigens of various kinds, thus they are dominated by T lymphocytes of the CD8 subpopulation. Antigen presenting cells (APC) are located on the surface of Peyer's patches. Antigen presentation by APC results in a number of processes, leading to the release of cytokines by Th1 (IFN- γ , IL-2) lymphocytes and Th2 (IL-3, IL-4, IL-5, IL-10, IL-13, GM-CSF) lymphocytes. As a result of the released cytokines activity, B lymphocytes switch to producing IgG₄ and IgE instead of IgG_{1,2,3} and IgM. Finally, the created E class antibodies connect to mast cells, leading to their sensitization.

According to the European Academy of Allergy and Clinical Immunology (EAACI), undesirable reactions to foods are classified on the basis of their pathogenesis. Abnormal reactions to foods have been divided into two groups – toxic and non-toxic. The first group includes all types of intolerance caused by the presence of toxic substances in foods, which are produced by pathogenic fungi or bacteria. The second group consists of all other types of food intolerances and allergies (Fig. 1) [3, 20].

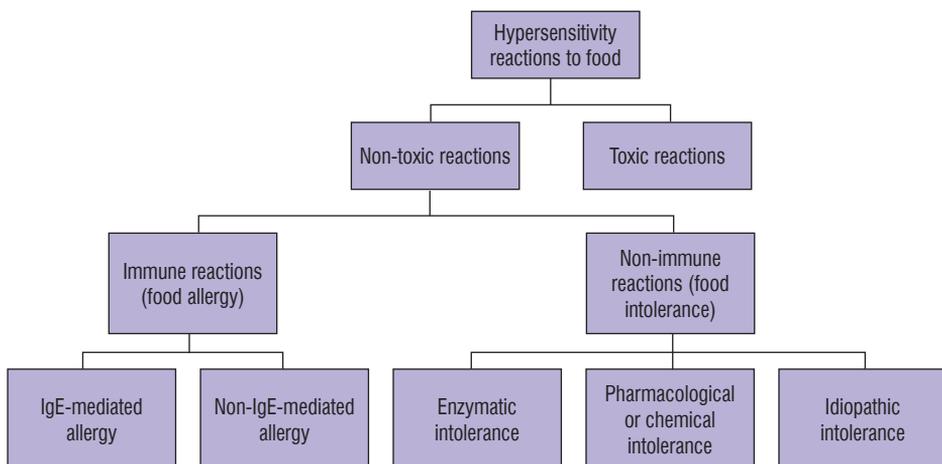


Fig.1. Food hypersensitivity scheme according to EAACI [7, 20]

In the 1960s Gell and Combs [4] differentiated four types of allergic reactions.

1. Type I (immediate, anaphylactic hypersensitivity) – an allergen interacts with IgE antibodies that bind with surface receptors on mast cells and basophils. As a result, histamine and cytokines are released.
2. Type II (cytotoxic hypersensitivity) – occurs as a result of IgG or IgM antibodies reaction to an allergen on the cell surface. In this type of hypersensitivity complement is involved, and the host cell is destroyed.
3. Type III (Arthus reaction or immune complex hypersensitivity) – as a result of the interaction of a free antigen with antibodies immune complexes are formed which then activate the complement and are deposited on tissues.
4. Type IV (cell-mediated response or delayed hypersensitivity) – the damage to the cells is caused by cytokines and a direct cytotoxic effect is mediated by macrophages and Th and Tc lymphocytes [4, 12].

Hypersensitivity is then a term applied to objectively repetitive symptoms occurring as a result of exposure to a specific stimulus; whereas, food allergy refers only to symptoms caused by IgE-mediated reactions (atopy) or non-IgE-mediated reactions which occur as a result of immune reactions. In clinical practice the terms “food hypersensitivity” and “food allergy” are used interchangeably to describe undesirable immune-mediated reactions to foods. According to the guidelines of the World Allergy Organization (WAO), these are two different diseases which are treated differently. Consequently, their differential diagnosis is extremely important. In normal circumstances, a specific antibodies class (IgE) is released as a response to a pathogen. Moreover, a properly functioning immune system guarantees the antigen tolerance, even at a very strong exposure. Foods including a potential allergen may cause various reactions in different people. Symptoms may occur immediately or may be delayed. Generally, three types of reactions are differentiated. The appearance of the symptoms shortly after food consumption is typical of IgE-mediated reaction, belonging to the first group. In the second group, patients exhibit subacute or chronic symptoms, depending on T lymphocytes. The last, third group, involves symptoms which occur immediately after food consumption and are chronic. It is believed that the reasons may be associated with abnormal humoral and cellular-mediated responses. This variety of symptoms and their durations are caused by the non-homogenous effects of allergens on patients. This means that one allergen may affect various people differently and may cause various reactions in one patient depending on the circumstances. Moreover, it is also known that one allergen may lead to various diseases in various people, and a natural history of food allergy exhibits changeable organ locations. Clinical manifestations involve skin, alimentary tract, respiratory system and, in extreme cases, anaphylaxis, including shock symptoms. Pathogenesis of an allergy is very complex. Actually, anyone, regardless of age, may develop an allergy. The appearance of this disease is largely dependent on exposure

to a specific allergen, i.e., how long and how intensely the allergen has affected the alimentary tract.

Acquiring tolerance in the course of food allergy, which underlies extinguishing an immune response to nutrition, is one of the most important mechanisms in the disease regression. It is associated with the alimentary system becoming more mature and “tighter”. Earlier reports indicated that allergies regress approximately at the age of 3. At present, it is believed that it may be occurring later. It is estimated that at the age of 4, approximately 11% of children acquire tolerance to hen’s egg allergens, and as many as 19% to allergic agents in cow’s milk. According to contemporary estimates, about 80% of patients do not exhibit allergic symptoms at the age of 16. It has been proved, however, that acquiring tolerance is not a constant phenomenon. The re-appearance of allergic symptoms in children who earlier tolerated a specific allergen has been observed (peanuts). The recurrence manifested itself in 5 out of 20 children following a break in in-taking this allergen [8].

The intensity of an allergic reaction depends also on the type of food processing. This may be connected with changes in protein conformation, stemming from the thermal processing of food, such as the Maillard reaction. It has been shown that in Western countries where roast peanuts are eaten, the incidence of sensitivity to this allergen is significantly higher than in, e.g., China where boiled peanuts are predominantly consumed. This is closely related with non-enzymatic glycosylation (the Maillard reaction), which occurs in an increased temperature. The reaction of amino acids with reducing sugars changes protein conformation, which affects their allergic potential. A similar reaction occurs in nutrition products (peanuts) which undergo the emulgation process. It has also been proved that the application of this type of technological processing leads to increasing the allergic potential of proteins, whereas boiling diminishes it. Research carried out thus far indicates that boiling also improves digestibility [8].

Food is not a lasting product, thus the continuing attempt to improve its quality and flavor as well as to maximize its shelf life. Consequently, various substances are added to food in order to gain the expected effects. Approximately 2900 substances of the aforementioned qualities are known at present. These additives, becoming food ingredients, may impact upon digestibility. The most frequent symptoms of allergy are rash and asthma, although cases of angioedema, rhinitis, headaches and behavioral disorders have been observed also. Numerous studies indicate that these clinical manifestations are caused by a relatively small group of additives, such as food colorings (azo dyes: tartrazine, red, sunset yellow and non-azo dyes: brilliant blue, erythroline and indigo), monosodium glutamate, preservatives, parabens, and sulfites [9].

Allergens have specific modes of acting. By interacting with the lymphoid tissue of the alimentary system, allergens can act in a variety of ways via IgE-mediated and non-IgE-mediated mechanisms. Thus, they can cause an allergic reaction via mastocytes degranulation; they can act by complement activation; they can affect arachidonic acid cascade; or can stimulate the formation of immune complexes due to their

ability to bind antibodies. It is very significant that these mechanisms do not need to occur simultaneously. It should be noted that IgE-mediated reactions amount to almost half of all immune-mediated allergic reactions, whereas this refers mainly to people genetically predisposed to producing this specific class of immunoglobulins as a response to contact with an allergen. Usually, IgE-mediated anaphylaxis regresses after 5–30 minutes following the food in-take, but in some patients the symptoms may appear as late as several hours following exposure to the allergen [2].

Varied tolerances to allergens are connected with the adaptation of the human organism to control their activities. Over the years the organism has formed protective barriers which significantly improve digestibility of these proteins. These barriers include the acidic environment of the stomach, digestive enzymes and microflora in the alimentary tract as well as mediators released by mast cells [3].

It is believed that up to 90% of IgE-mediated food allergies are caused by eating specific types of foods, both animal-derived and plant-derived foods. The main sources of antigens are cow's milk proteins, soybean, hen's eggs, peanuts, wheat, tree-nuts, and seafood [13, 18, 21]. Apart from cow's milk, hen's eggs are the most common food allergen. This is significantly influenced by eggs being commonly eaten, and used in cakes, meats, sauces, salads and creams as additives. It is also important that egg whites improve the nutritional value of meals [5, 21].

Typical symptoms of an allergy to egg whites include: stomach ache, urticaria, pruritus, atopic skin inflammation (ASI), vomiting, and less frequently rhinitis, conjunctivitis or laryngeal edema. In extreme cases strong anaphylactic shock may occur. The intensity of degree of the symptoms may be varied. An acute allergy was diagnosed in a young woman who manifested the symptoms having used the knife which had been previously used to break an egg to spread butter on bread. Moreover, this person could not be in a room in which there were freshly broken eggs. Another strong reaction to exposure to an antigen is exemplified by a man who applied for a certificate confirming his allergy in order to present it to an army medical board. An extremely strong hypersensitivity was diagnosed; a case of an anaphylactic shock after using a not fully washed spoon which had been used by someone else to eat scrambled eggs was confirmed. Cases of milder allergy are also known. In a 6-month old boy eating an egg caused pruritus and skin inflammations. Removing the allergen from the diet improved his condition. At a later age, the boy could not eat more than two eggs at one sitting since this caused diarrhea [5, 14, 15].

Allergens from hen's eggs may be found in the milk of those mothers who included eggs in their diet. This is exemplified by a case of a boy who was exclusively breast-fed from birth. At the age of 4 months he ate an egg for the first time, which resulted in the appearance of exudative lesions and erythematous foci. After 48 hours he was diagnosed with ASI [5, 14].

Further, it is believed that antigens from hen's eggs may cause allergies in workers employed in egg processing plants. Measurements in the plant were taken which

confirmed the presence of allergens in the air, not only in primary areas but also in office rooms. The risk of dangerous allergic reaction exists also for allergic people who are administered a vaccine produced on the basis of hen eggs [5, 9].

Milk, as a diet component, has accompanied human beings since ancient times. The first reports about its adverse effects for human health appeared during those times. Hippocrates mentioned various reactions of people to eating cheese. Cow's milk harbors approximately 20 proteins of an allergic potential. The most important allergens deriving from milk include casein and whey proteins, i.e. β -lactoglobulin, α -lactoalbumin, and bovine serum albumin. Caseins from the milk of related species of mammals differ from each other to a larger degree than whey proteins. Moreover, it should be noted that thermal processing does not entirely eradicate the allergic properties of these proteins. The total disappearance of these qualities following pasteurization or boiling is only observed in bovine serum albumin. It was generally believed that cow's milk allergy is strictly a food allergy; however, recently, cases of contact and inhaled allergies have been noted in clinical practice. Typical symptoms of cow's milk allergy involve: diarrhea, vomiting, urticaria, atopic skin inflammation, and respiratory complications. Approximately 10% of patients develop anaphylactic reactions [1, 10, 11, 16, 22].

The last group of animal-derived food allergens includes those derived from fish and crustaceans. This group is exceptionally important. Owing to the examination of proteins from fish tissue, in 1921 Prausnitz and Kustner proved the existence of the factor which was years later called IgE immunoglobulin. Moreover, they examined the protein which was later to become the first sequenced allergen, officially called Gad c1 [17, 22].

Fish allergy is very often concurrent with crustacean allergy and other seafood allergies. Whereas in Poland crustaceans are not very popular as diet ingredients, in other countries shellfish allergies are a major problem. In the Unites States alone, about 30 species of shellfish are eaten (shrimps, rock lobster, lobster, crabs, and crayfish) [22].

Fish more frequently lead to allergies in children than in adults, although children less often develop cross-reactive allergies. A characteristic feature of a cross-reactive allergy is that it does not regress with age, although a clinical case of a patient is known, with a constantly detected allergy between 5 and 60 years of age, whilst at the age of 78 no allergic reaction to this type of food was observed.

Both saltwater and freshwater fish may lead to sensitivity. It depends on the availability of a particular species, climate and a cuisine tradition with respect to such foods. Allergies to this type of food are relatively easily diagnosed, since most often food allergy is observed in synergy with inhaled allergy. In Poland this medical problem is relatively rare as the consumption of this type of food is rather limited [1, 10, 16, 22].

Conducted research indicates that constant social development worldwide significantly affects the incidence of allergy. It is estimated that at present this problem

involves 2–8% of children and 1–2% of adults. It has been proved that children usually “outgrow” their allergies. An annual number of food allergy cases in children diminishes with an increase in age: from 10% (in children below 1 year of age) to 3% (in 6-year-old children) [6, 13].

Unfortunately, diagnosing food allergy remains a major problem. It is a complicated and complex process, involving an accounting of many concurrent factors. A medical interview is a very important diagnostic tool. It is necessary to regard the period which has passed between the consumption of the suspected food and the appearance of the symptoms, the amount of consumed food and the concurrence of other factors, such as effort, alcohol, medication, diet, traveling, etc. The golden mean in diagnostics is a double-blind, placebo controlled test, a food provocation. A positive result allows one to determine the harmful factor, but it does not explain the pathomechanism of food allergy. In order to detect the cause of IgE-mediated allergy, prick skin tests or allergen-specific IgE antibody tests are carried out. Negative results confirm the absence of IgE-mediated reaction in 90% of the cases; however, the positive results do not prove that a given allergen does not cause the symptoms. The assessment of the size of the skin reaction also cannot be treated as an indicator as to which allergen causes sensitivity. It has been proved that the size of skin reactions does not correlate with the symptoms' intensity. Food allergy diagnostic procedures also include atopy patch tests, especially when the outset of the disease is delayed. However, the evaluation of such tests results is at present both difficult and ambiguous [8].

It has been shown that specific groups of allergens reveal their allergic properties under favorable conditions, e.g., oral allergy syndrome is caused by cross-reactions, whereas anaphylaxis connected with effort and food consumption appears as a result of IgE-mediated mechanism (first food consumption, then effort). This mostly refers to youth and adults, and the allergens involved are, among others, wheat, seafood, and celery [8].

Similarly to the difficulties involved in diagnosing food allergy, its treatment is also complex. Avoiding food that affects a given patient remains the basic treatment procedure. Educating the patient seems to be exceptionally important. It entails enumerating those foods which contain allergens. Pharmacological treatment is adapted to the occurring symptoms. Most frequently, second generation antihistamines are administered, recommended for such medical conditions as urticaria, acute oral allergy or ASI. Patients at risk of anaphylaxis should be definitely provided with an auto-injector with adrenaline and taught how to apply the medication to themselves.

CONCLUSIONS

1. Allergy, due to a variety of symptoms and their intensities, is a significant diagnostic and therapeutic challenge for modern societies.
2. Since allergy affects both children and adults, as well as exhibiting increasing incidence trends, it fulfils the criteria established for civilization-related diseases.

3. Since social awareness with respect to this medical condition and its outcomes is still insufficient, it is necessary to disseminate information concerning this disease.

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