Hypersensitivity Reactions to Food Additives

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Food additives (FAs) are commonly used in prosscessed foods, but hypersensitivity reactions to food additives (HFA) appears to be a rare phenomenon. Identification of the FA responsible for hypersensitivity and its treatment is difficult. Diagnosis is a challenge for the clinician and for the patient. A food diary is a helpful diagnostic tool. It allows diet therapy to be monitored based on the partial or complete elimination of products containing a harmful additive. An elimination diet must not be deficient, and symptomatic pharmacotherapy may be necessary if its application is ineffective.

Keywords: allergy ; hypersensitivity ; food additives functions ; consumer safety ; therapy

1. Introduction

With the development of the food industry, food additives have become ingredients of processed foods. For decades, food hypersensitivity reactions incident to the consumption of food products containing these substances have been observed. Unfortunately, the data on hypersensitivity related to the consumption of additives often come from a few studies involving small groups within the population; some of them are even casuistic papers, and they are mostly from the last decades of the previous century [1][2]. The results presented by other researchers are inconclusive and do not answer the question of whether a relevant additive may induce hypersensitivity reactions; therefore, this issue remains open. Simultaneously, it is not always known whether food additives cause hypersensitivity or exacerbate the symptoms of an existing disease, or whether the coexistence of several variables is necessary for adverse effects to occur.

Even though over a decade has passed since the publication of the classification of adverse food reactions by NIAID, the terms food allergy and hypersensitivity [3] are still used alternately, even in the professional literature, which is not always reasonable regarding the pathomechanism of a relevant disease. To a high degree, this is caused by the fact that the problem of additives in the context of how they induce unwanted symptoms is complex. It seems that hypersensitivity to food additives (HFA) is mainly related to the advancement of atopic skin diseases [2]. There are also known cases of contact dermatitis (type IV allergic reactions) after occupational exposure to additives [4][5][6][7][8], or the use of cosmetics in which the same additives may be present as in food [9][10][11]. Therefore, it should be noted that some food additives or their metabolites cause allergic reactions and others cause non-allergic ones. However, this mechanism is often not fully understood. In addition, although there is no evidence for this, many additives have been reported to lead to symptoms of food hypersensitivity [12][13].

2. Epidemiology and Pathomechanism of HFA

Only some people are hypersensitive, and only to certain food additives—this means that not all foods containing food additives should be automatically excluded from the diet. For example, monosodium glutamate occurs naturally in sardines or parmesan cheese, and at a much higher concentration than when used as a food additive. Other ‘natural chemicals’ causing allergies or intolerances include nuts and seafood [12]. The frequency of reactions to food additives is estimated at less than 1% of the total number of food hypersensitivity reactions in adults and up to approximately 2% in children.

According to Kołodziejczyk et al. [14], HFA occurs in 0.5% of the general population and slightly more often in the atopic population. Moreover, Pałczyński suggests [15] that HFA is more common in some cohorts, e.g., in 25% of patients with a food allergy, 10–20% patients with IgE-dependent bronchial asthma, 5–10% patients with aspirin intolerance and 5–10% patients with chronic urticaria. According to other data, while the prevalence of food allergy in the general population is estimated at 5% [16], HFA is about 0.026% [17]. The lack of knowledge of their exact number is related to the difficulty in recognising them—it should be noted that hypersensitivity to food (also confirmed by a provocation test) is much less common than is shown in medical histories, and atopy is not a known risk factor for HFA [18].

Exposure to food additives is attributed to numerous symptoms, but the actual cause-and-effect relationship has not yet been well proven. Reactions to food additives should be suspected in patients who have been ruled out for a food allergy and who report symptoms after eating a variety of unrelated foods—especially when they concern store-bought food and do not include the same food prepared at home.

The pathomechanism of the reaction to food additives should allow for both the allergic background (with the dominant IgE-independent pathway) and the non-allergic background (toxic and immunotoxic—shown in **Table 1**) [19][20]. Symptoms caused or exacerbated by food additives are usually less dramatic than those caused by IgE-dependent allergic reactions, which also suggests mechanisms of non-IgE-dependent intolerance or allergy [21]. In a review study by Gostner at al. [22], it was shown that in vitro, not only typical antioxidants (e.g., vitamin C, E, resveratrol), but also some preservatives (i.e., sulphites, benzoates) and curcumin dye, enhance a suppressive effect on the activation of Th1 cells in freshly isolated human peripheral blood mononuclear cells, and additionally reduce the number of pathogens to which people are exposed. This process shows that antioxidants have an anti-inflammatory property, but on the other hand could shift the immune balance towards Th2-type immunity, which is an important pathway in allergic reactions. Because dietary habits and FA use have changed drastically, an increased tendency towards allergy and asthma in the Western world might be observed. The occurrence of symptoms, their nature and intensity are also influenced by so-called modulating factors, which include the amount and form of the consumed allergen, frequency of its consumption, cumulative effect and additional trigger mechanisms (physical activity, consumption of coffee or alcohol, menstruation) [23].

Table 1. Types and characteristics of hypersensitivity reactions Own elaboration based on [20].

Type of Reaction	Type of Antigen	Involved Antibody or Cytokine	Involved Cells or Receptors	Example of Reaction
Type I	Soluble	IgE	Mast cells	Anaphylaxis, allergic rhinitis
Type II	Matrix- or cell-associated	IgG	Fc receptor and NK cells, phagocytes	Thrombocytopenia
Type III	Soluble	IgG	Fc receptor and complement cells	Arthus reaction
Type IVa	Direct T-cell stimulation or antigen presented by cells	IFN-γ, TNF-α	Macrophages	Contact dermatitis
Type IVb	Direct T-cell stimulation or antigen presented by cells	Il-5, Il-4 or Il-13	Eosinophils	Persistent asthma
Type IVc	Direct T-cell stimulation or antigen associated with cell	Perforin or granzyme B	T-cells	Contact dermatitis
Type IVd	Direct T-cell stimulation or soluble antigen presented by cells	GM-CS, CXCL8	Neutrophils	Stevens–Johnson syndrome

3. The Role and Types of Food Additives

There are over 300 food additives allowed for use in EU countries. According to the definition provided by Regulation (EC) No. 1333/2008 of the European Parliament and of the Council of 16 December 2008 on food additives, food additives ‘shall mean any substance not normally consumed as a food in itself and not normally used as a characteristic ingredient of food, whether or not it has nutritive value, the intentional addition of which to food for a technological purpose in the

manufacture, processing, preparation, treatment, packaging, transport or storage of such food results, or may be reasonably expected to result, in it or its by-products becoming directly or indirectly a component of such food' [24].

Food additives enable a reduction in the cost of food production and increase its efficiency, at the same time improving the food's microbiological safety and chemical stability and giving it the appropriate organoleptic features. Currently, the topic of the health impact of food additives is still controversial and many myths have arisen around it, supported by easy access to information of dubious origin [23].

In the EU countries, EFTA, GCC, South Africa, the U.K., Australia, New Zealand, Malaysia, Hong Kong, India and Israel, as well as in the USA, appropriate numerical markings preceded by the letter 'E' are used for individual categories of food additives, depending on their technological function, and mainly in products of European origin. The scheme below (**Table 2**) presents a short description of the groups of food additives based on the Regulation (EC) No. 1333/2008 of the European Parliament and of the Council of 16 December 2008 on food additives. It should be noted that, contrary to popular opinion, compounds with an E-number include not only fully synthetic food additives, but also those that are obtained from natural raw materials, or are synthetic but identical to natural ones [24].

Table 2. Groups and technological functions of food additives. Own elaboration based on [24].

Group of Additives	Functions
Food dyes	They give a new or more attractive colour to food products. There are natural (including those identical to natural) and synthetic dyes. The dyeing ability and the durability of the colour of natural dyes depend on environmental factors. Synthetic dyes (organic and inorganic) allow obtaining a permanent colour, are cheaper and have a standard dyeing strength.
Preservatives	They prevent the occurrence of physical, chemical and biological changes in food, which affect the attractiveness and shelf life of food, thus extending it. They affect the structure and functions of microorganism cells and show mutagenic properties in relation to them. Their effectiveness is influenced by environmental conditions. Their activity depends on the type and strain of microorganisms. They are effective at concentrations < 2‰. Some of them give a sour taste to products.

Group of Additives	Functions
Antioxidants, acids and acidity regulators	Antioxidants counteract the disadvantageous oxidation reactions of chemical compounds present in food products. Antioxidants include common antioxidants, substances with antioxidant properties in addition to other properties, and synergists. They must demonstrate the ability to maintain durability during technological processes. Acidity regulators and acids influence the acidity of food products.
Thickening agents, emulsifiers, emulsifying salts, leavening agent, moisture retainers and gelling agents	Thickening agents—allow obtaining the appropriate adhesiveness of food products. Emulsifiers—participation in the formation and/or maintenance of emulsions. Emulsifying salts—allow the homogeneous distribution of fats in cheeses through the dispersion of proteins. Some of them (as well as some preservatives and acidity regulators) increase the volume of products by releasing gases—the so-called leavening substances. Some keep the product moist, which prevents it from drying out. Gelling substances—giving food products in the form of a gel an appropriate consistency.
Anti-caking agents	They prevent food particles from sticking together.
Flavour enhancers	They intensify the flavour and the scent.
Sweeteners, glazing agents and others	The sweetness of sweeteners is close to or many times greater than that of sucrose. They are divided into natural, synthetic and semi-synthetic; the latter two types are used as food additives. Glazing agents allow the product to shine and protect its outer layer. Others include substances that contribute to the formation or prevention/reduction of foam formation.

Group of Additives	Functions
Stabilisers and other additives	They allow maintaining the physical and chemical properties of food products. Carriers—enable the use of other substances by physically modifying food additives. Modified starches—starches subject to chemical modification, mainly used as thickeners. Packing and carrying gases—protect food against spoilage or enable stuffing products out of the packaging. Sequestrants—create chelates with metal ions, thus improving the oxidative stability of food and its quality. Improvers—improve the baking value of flour. Binding substances—help maintain the proper firmness of vegetables and fruit, facilitate the formation of gel synergistic effect for gelling substances. Bulking agents—increase the volume of the product.

4. Adverse Reactions to Food Additives

Symptoms of HFA may affect one or more organs. The reaction to an allergen occurs up to 2 hours after its ingestion (early reaction), up to 12 hours after exposure (delayed reaction) or more than 12 hours after contact with the allergen (late reaction). The symptoms of food hypersensitivity concern not only the gastrointestinal tract, but may also affect the skin, respiratory system, central nervous system and circulatory system [25]. The most common clinical manifestations of reactions to food additives are chronic urticaria and angioedema, and, less often, anaphylactic reaction, an exacerbation of symptoms of atopic dermatitis, bronchial asthma or allergic rhinitis. In sensitive individuals, oral or local exposure may also cause several non-specific symptoms, such as paroxysmal facial flushing, hypotension, abdominal pain, deregulation of bowel movements, itching of the skin and tachycardia [26][27].

5. Diagnosis and Treatment

Due to the increasing number of substances added to food, as well as many possible pathomechanisms of their action, HFA is hard to diagnose and it is hard to statistically estimate its incidence. The basic role here is a detailed medical interview aiming to establish a cause and effect relationship between the onset of symptoms and the meal consumed.

A food diary may be a helpful tool in determining the cause of HFA symptoms and in further work with a patient suspected of such hypersensitivity. In this diary, the patient should write down what food products and dishes they consumed during the day, as well as their weight and volume expressed in home measures (e.g., glass, handful, plate, tablespoon). In addition, if possible, the patient should also write down the recipes of the consumed dishes and paste labels with the ingredients of the purchased products to it, in order to determine more precisely what may be the cause of their ailments. Any symptoms observed should also be recorded in this diary.

Skin-prick tests and the level of serum-specific IgE-antibody concentrations are commonly used in the diagnosis of food allergy, but they do not take into account preservatives added to food. In patients suspected with hypersensitivity to these preservatives, the ‘diagnostic gold standard’ is an oral challenge test with a DBPC trial—this test should be performed in a hospital ward [28][29].

Food additives are used in the amounts necessary for technological reasons. Food hypersensitivity induced by food additives is not a frequent clinical phenomenon, and its origin is unclear. An important issue related to HFA is the limited number of studies involving hypersensitive people that would enable clarification of the frequency of this type of hypersensitivity. However, if the patient’s hypersensitivity is confirmed, it is reasonable to follow a diet that eliminates additives that contribute to the occurrence of certain symptoms. Sometimes, this will mean the complete elimination of the

additive, while sometimes it may be sufficient to limit it to a certain amount that is tolerated by the patient. However, such a diet cannot turn out to be deficient; hence, the care of a dietitian specialising in the diet therapy of this type of diseases is necessary. If such a procedure does not bring the expected results, the patient is at risk of severe reactions, or if the damages resulting from its use outweigh the benefits, symptomatic pharmacotherapy should be introduced [18].

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