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Review

Hypersensitivity reactions to food and drug additives: problem or myth?

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Summary. *Background and aim of the work:* The possibility of an allergic reaction or an intolerance to additives is frequently suspected by parents, especially for chronic illness with frequent exacerbations such as atopic dermatitis or chronic urticaria. For more than 50 years, potential adverse reactions to additives have been suggested, but to date data are conflicting. The purpose of this article is to provide the clinicians with general information about additives and adverse reactions to them and to suggest a practical approach to children suspected to have reactions to food additives. *Methods*: We performed an extensive research on all English-language Medline articles, case reports and reviews published online until December 2018. Used search terms were: food additives, food dye, adverse reactions, food allergy, food hypersensitivity, intolerance, drugs, children. *Results*: There are only few case reports of adverse reactions in childhood with a clear involvement of additives. In this review article we reported the associations between additives and adverse reactions described in literature, in order to inform the pediatrician about the potential clinical manifestations. *Conclusions*: Prior to suspect an adverse reaction to additives, it is important to rule out other possible causes: the diagnostic process is complicated and rarely conclusive. The gold standard is the double-blind placebo controlled oral challenge after an exclusion diet. (www.actabiomedica.it)

Key words: food additives, food dye, adverse reactions, food allergy, food hypersensitivity, intolerance, drugs

Introduction

Additives are substances used in the food industry for many purposes, such as to preserve food, to improve its taste or appearance. The earliest record of a food additive date from the ancient Egypt, around 1500 BC, when natural extracts were added to candies to make them more appealing (1).

The Food and Drug Administration (FDA) updates an online list of these food additives that nowadays includes more than 3000 substances (*https://www.fda.gov/food/ingredientspackaginglabeling/foodadditivesingredients/ucm094211.htm*). Prior their use in foods, they must pass a premarket safety evaluation in accordance with a specific food additive regulation from specific government agencies, such as the FDA in the United States or the European Food Safety Authority (EFSA) in Europe (2).

A specific group of food additives named "Generally Recognized As Safe" (GRAS) includes about 1000 substances that are considered safe by experts and are exempted from the usual tolerance requirements (3).

The widespread use of additives has caused concern among consumers about the possibility of adverse reactions, but few scientific data are available. Recently, the American Academy of Pediatrics (AAP) has given rise to doubts regarding the safety of GRAS in children (4).

The purpose of this article is to provide the reader with general information about food and drug additives and adverse reactions to these substances and to suggest a practical approach to children suspected to have reactions to additives.

Definitions of food additives and classification

Food additives are defined according to their specific functions. Several definitions are available, that are similar to each other (Table 1).

According to the Joint FAO/WHO Expert Committee on Food Additives (JECFA), an international expert scientific committee administered jointly by the Food and Agriculture Organization of the United Nations (FAO) and the World Health Organization (WHO), food additives are "substances added to food to maintain or improve its safety, freshness, taste, texture, or appearance".

The definitions used by the FDA and the EFSA point out that these substances are added to food intentionally.

Food additives generally have the following characteristics: 1- synthetic and natural substances; 2- they cannot be consumed alone as food themselves; 3- the purpose of addition is to improve the quality, color, fragrance, flavor of food, and to meet the demands of preservation, freshness and processing (1).

More than 3000 food additives are listed by the FDA, and they can be classified into different groups according to their function and property: preservatives, sweeteners, color additives, flavors and spices, flavor enhancers, fat replacers, nutrients, emulsifiers, stabilizers and thickeners, binders, texturizers, pH control agents and acidulants, leavening agents, anti-caking agents, humectants, yeast nutrients, dough strengtheners and conditioners, firming agents, enzyme preparations, gases.

Some substances used as food additives can also be contained in some medications or cosmetics. Children suspected to have an adverse reaction to a food additive might need to avoid medicines and cosmetics that contain them.

Additives can be found in all kinds of food and beverages (Table 2). In 2011, EFSA provided a list of food in which additives cannot be used (Table 3) (5).

Epidemiology

To date, few studies have investigated the prevalence of adverse reactions to food additives. Contrary to the general public perception, the prevalence of these reactions seems to be rather low.

According to some studies the prevalence in adults is estimated to be less than 1%, while it seems to be higher in children (1-2%) (6-8). Atopic children appear to be more likely to have adverse reactions to food additives (7, 9).

The estimated low prevalence of adverse reactions to food additives contributes to make the diagnosis a true challenge for the clinician.

Table 1. Main definitions of food additives by different government agencies

Last updated on January 31, 2018	United States	JECFA www.who.int	Substances added to food to maintain or improve its safety, freshness, taste, texture, or appearance.
Last updated on February 7, 2018	United States	FDA www.fda.gov	Any substance the intended use of which results or may reasonably be expected to result - directly or indirectly - in its becoming a component or otherwise affecting the characteristics of any food.
Last updated on November 30, 2018	Europe	EFSA www.efsa.europa.eu	Food additives are substances added intentionally to foodstuffs to perform certain technological functions, for example to colour, to sweeten or to help preserve foods.
Last updated on March 18, 2012	Europe	EAACI www.eeaci.org	Food additives are a large and varied group of substances added to food to, for example, prevent growth of microorganisms, give colour or flavour, improve texture or prevent browning.

Table 2. Main additives in foods and beverages

Substances	Foods and beverages
Food colorants[§]	
Carmine*	Cheese, fruit and vegetable preparations, jams, chewinggum, breakfast cereals, meat products (salami, sausages), processed fish and fishery products, soups, sauces, dietary products, desserts, snacks, alcoholic and non-alcoholic drinks.
Annatto*	Cheese, breakfast cereals, processed fish and fishery products, desserts, jams, processed potato products, meat products, soups, sauces, noodles.
Tartrazine	Cheese, canned or bottled fruit or vegetables, soups, processed fish or fishery products, pickles, desserts, sauces, seasonings, flavoured processed cheese, dietary products, non-alcoholic flavoured drinks.
Spices*	Pudding and pie fillings, gelatin dessert mixes, cake mixes, salad dressings, candies, soft drinks, ice cream and sauces, Asian dishes
Saffron	Soups, bouillabaisse, sauces, rice dishes (paella, "risotto alla milanese"), cakes, cheese, liqueurs
Preservatives	
Butylated Hydroxyanisole, Butylated Hydroxytoluene[§]	Cereal-based snack foods, cereals, soups, sauces, dehydrated meat, dehydrated potatoes, chewing gum, seasonings and condiments, fats and oils, cake mixes
Sulfites*[§]	Dried fruits, fresh fruits, frozen fruits, canned or bottled fruit and vegetables, fruit and vegetable preparations, jam, processed potato products, cereals, starches, meat preparations (sausages), processed fish and fishery products, seasoning and condiments, snacks, desserts, fruit juices, flavored drinks, wine, beer, other alcoholic drinks.
Sweeteners	
Aspartame[§]	Canned or bottled fruit and vegetables, jam, chewing gum, breakfast cereals, processed fish and fishery products, soups, sauces, dietary foods, beer and malt beverages, soft drink, diet soda, desserts, snacks.
Flavor Enhancers	
Monosodium glutamate (MSG)	Processed cheese, fats and oils, fruit and vegetable preparations, processed potato products, cocoa and chocolate products, chewing gum, breakfast cereals, gluten-free and hypoproteic pasta, noodles, bread and rolls, processed fish and fishery products, processed eggs and egg products, seasonings and condiments, soups, sauces, dietary foods, glute-free products, non-alcoholic and alcoholic beverages, desserts, meat products.

[§] These additives can also be found in medications.
* These additives can also be found in cosmetics.

Reactions to food additives

Food hypersensitivity is defined as an adverse reaction to food or a food additive and can be mediated by two different mechanisms: immunologic and non-immunologic.

Immunologic reactions are divided into 3 groups: IgE-mediated (allergic reactions), non-IgE mediated (cell-mediated) or both.

On the contrary, non-immunologic reactions do not involve the immune system and they are also defined "food intolerances". They subtend metabolic, pharmacological, toxic and undefined mechanism.

IgE-mediated reactions are quite uncommon but can be severe and life-threatening. Natural additives contain molecules of sufficient molecular weight to induce an IgE-mediated response (10). On the contrary, synthetic additives are more likely to act like haptens, because of their low molecular weight. Haptens can induce an IgE-mediated response only if they are attached covalently to a large carrier molecule (10).

Table 3. Foods in which the presence of an additive may not be permitted according to EFSA (EU Commission 2011) (5)

"Unprocessed foods" (a food which has not undergone any treatment resulting in a substantial change in the original state of the food, for which purpose the following in particular are not regarded as resulting in substantial change: dividing, parting, severing, boning, mincing, skinning, paring, peeling, grinding, cutting, cleaning, trimming, deep- freezing, freezing, chilling, milling, husking, packing or unpacking)
Honey
Non-emulsified oils and fats of animal or vegetable origin
Butter
Unflavoured pasteurised and sterilised (including UHT) milk and unflavoured plain pasteurised cream (excluding reduced fat cream)
Unflavoured fermented milk products, not heat-treated after fermentation
Unflavoured buttermilk (excluding sterilised buttermilk)
Natural mineral water and spring water and all other bottled or packed waters
Coffee (excluding flavoured instant coffee) and coffee extracts
Unflavoured leaf tea
Sugars
Dry pasta, excluding gluten-free and/or pasta intended for hypoproteic diets

Clinical manifestations

The spectrum of clinical manifestations is variegated. Most of the studies investigated adverse reactions to food in adult population and little is known about these manifestations in children.

Food additives can be responsible of the onset of new symptoms, ranging from *mild* manifestations (i.e. flushing or rhinorrhea) to life-threatening situations (i.e. anaphylaxis), or can be the cause of worsening pre-existent diseases, such as atopic dermatitis (AD).

The manifestations caused by a specific food additive can vary from patient to patient.

Food dyes are usually added to food, beverages, medications and cosmetics to make them more appealing and/or to enhance their color. They have been associated with many adverse reactions, mainly described in adults. Few studies are available about these reactions in children.

Carmine, a natural red dye, has been implicated in urticaria/angioedema, recurrent intermittent bouts of generalized systematized dermatitis (11), asthma (12, 13, 14) and anaphylaxis (15-17) in adults.

Two studies (11, 18) reported carmine as cause of intermittent flares of atopic eczema (AE) in children.

Annatto is a deep yellow or orange food coloring which is added to food and cosmetics. To our knowledge, only two studies have reported adverse reactions to this additive in children, consisting both in urticaria and angioedema (19, 20). In adults, the potential role of Annatto in inducing anaphylaxis has been described (21).

Tartrazine has been frequently linked to different illnesses such as Chronic Idiopathic Urticaria (CIU), recurrent intermittent flares of AE and fixed drug eruption in children (22-25). In 2003 Nettis et al. found that, in adults, the percentage of acute urticaria and/or angioedema induced by tartrazine, investigated with a Double Blind Placebo Controlled Food Challenge (DBPCFC), is very low (about 1%) (26).

The ingestion of tatrazine was also associated with irritability, restlessness and sleep disturbance in some children, with a dose-response effect (27).

Spices are usually added to pudding and pie fillings, gelatin dessert mixes, cake mixes, salad dressings, candies, soft drinks, ice cream and sauces.

Exposure to spices is highest in adults than in children with a particular frequency in certain occupa-

tions, such as spice factory workers, butchers, bakers, chefs, restaurant workers, and florists (28).

In adults, spices seem to be responsible of: a) irritant effects (i.e. irritant contact dermatitis, sneezing, rhinorrhea, ocular itching, conjunctival injection, tearing, or cough); b) IgE-mediated reactions (i.e. rhinoconjunctivitis, asthma, urticaria, angioedema, anaphylaxis, gastrointestinal symptoms); c) Non IgE-mediated immunologic reactions (i.e. allergic contact dermatitis) (28).

Spices-induced angioedema and anaphylaxis have been described in children (29-31) and spices seem to be also responsible of exacerbations of AE in children (32).

Saffron, which is widely used as spice or as coloring agent, was associated to symptoms of allergic rhinoconjunctivitis (sneezing, rhinorrhea, nasal obstruction, and conjunctivitis) in a 12-year-old boy, after performing a DBPCFC (33).

Preservatives are commonly added to prevent food spoilage and changes in food color, flavor and texture. Butylated Hidroxyanisole (BHA) and Butylated Hydroxytoluene (BHT) are useful preservatives due to their antioxidant capacity. They have been associated with exacerbations of CIU in studies involving adult patients (34-36). BHT can also be found in some medications, such as multivitamin (oral suspension) or in resin-based dental sealants (37, 38). To our knowledge there are no studies or case reports about adverse reactions to BHA or BHT in children.

Sulfiting agents in the form of sodium salts (i.e. sodium metabisulfite) and potassium salts (i.e. potassium bisulfite) are used as preservatives in the food and pharmaceutical industries. They reduce microbial spoilage and act as an antioxidant in some medications.

Sulfite sensitivity occurs more often in asthmatic patients (39). In adults, dermatologic, respiratory and gastrointestinal manifestations have been described, such as contact dermatitis (40), bronchoconstriction (41) and abdominal cramps with diarrhea (42). Bronchoconstriction has been described, with a greater frequency in adults than children (39, 43, 44). Recently, recurrent events of urticaria and angioedema following sodium metabisulphite ingestion in a five-year-old female has been described (45). Sulfites contained in medicines and cosmetics can be also responsible of adverse reactions (37, 46).

Sweeteners are food additives used to improve sweetness with or without extra calories. Aspartame is an artificial sweetener present in several sugar-free products, as well as in some medications and vitamin supplements. A case study conducted in a 11-years-old patient, demonstrated the resolution of Systemic Contact Dermatitis (SCD) after dietary restriction, cessation of montelukast chewable tablets (which contained aspartame) and all personal health products containing aspartame (47). Studies in adults showed a correlation between daily aspartame intake and chronic headache, but this was not confirmed among children (48, 49, 50). A recent study found a correlation between consumption of aspartame in artificially sweetened soft drinks and early menarche (51).

Monosodium Glutamate (MSG) is a flavor enhancer and it is used in many processed foods. It is included in the GRAS group by the FDA classification. In 2017, EFSA re-assessed the safety of glutamates used as food additives and derived an acceptable daily intake (ADI) (*https://www.efsa.europa.eu/en/efsajournal/pub/4910*).

In 1968, MSG was associated to the well-known 'Chinese restaurant syndrome' characterized by several symptoms, such as tightness, burning or numbness in the face, neck and upper chest (52).

MSG have been considered responsible of many manifestations in adults, such as exacerbations of unstable asthma (53) or CIU (54, 55). Over the last two decades, some studies investigated the relation between MSG ingestion and asthma or bronchospasm in adults, but with conflicting results (56). No studies have been conducted on children about the role of MSG in exacerbate chronic asthma. In 2012 a Cochrane review about MSG and chronic asthma in adults and children concluded that there is no evidence to support the avoidance of MSG in all patients (57).

MSG has been associated with CIU not only in adults, but also in children (22, 58). In 2000, Simon demonstrated that MSG is an unusual (<3% at most) exacerbant of CIU in adults (59).

Table 4. Most common food additives and their adverse reactions in children.

Food colorants	
Carmine	Recurrent intermittent flares of atopic eczema (11, 18)
Annatto	Urticaria/angioedema (19, 20)
Tartrazine	Recurrent intermittent flares of atopic eczema (24) Chronic Urticaria (22, 23) Fixed drug eruption (25) Irritability, restlessness and sleep disturbance (27)
Spices	Angioedema and anaphylaxis (29; 30; 31) Exacerbations of AE (32).
Saffron	Allergic rhinitis (33)
Preservatives	
Butylated Hidroxyanisole, Butylated Hydroxytoluene	No studies in children.
Sulfites	Bronchoconstriction (43, 44) Urticaria and anaphylaxis (45)
Sweeteners	
Aspartame	SCD (47) Chronic headache (not confirmed in children) (48, 49, 50) Early menarche (51).
Monosodium glutamate	CIU (22, 58)

Reactions to drug additives

Additives can also be added to medicinal products as excipients. An excipient is any component of the medicinal product other than the active substance. Excipient can be found in any medicinal product and every excipient can be responsible of hypersensitivity reactions to the specific drugs.

Food dyes can be easily found in many drugs. Tartrazine is a food dye that has been associated with hypersensitivity reactions. The first report of a reaction to drugs containing tartrazine was in 1959 (60). It is thought that these reactions, occur most commonly in patients with acetylsalicylic acid (ASA) sensitivity (61). As it is described for tartrazine added to food, this food dye contained in medications can cause urticaria and/or angioedema (60-62).

A fixed drug eruption to tartrazine in children has been also described (25).

One of the most widely used drug excipient is lactose. It is used as a stabilizing agent, for example in inhaled corticosteroids, daily used for patients diagnosed with asthma. Even if rarely, a life-threatening event can occur after using one of these medications containing lactose in patients with cow's milk protein allergy (63). In literature, only one case describes anaphylaxis after the use of lactose-containing inhaled corticosteroids (64). More recently a case of refractory asthma exacerbation in a child with cow's milk protein allergy resulting from a hypersensitivity reactions to lactose-containing medications, has been described (63).

Among sweeteners, aspartame can be used as an excipient in some medications such as montelukast chewable tablets. A case study conducted in a 11-years-old patient, demonstrated the resolution of Systemic Contact Dermatitis (SCD) after dietary restriction, cessation of montelukast chewable tablets and all personal health products containing aspartame (47).

Parabens are aliphatic esters of parahydroxybenzoic acid and include methyl, ethyl, propyl, and butyl parabens. Sodium benzoate is a closely related sub-

stance usually reported to cross-react with the other compounds noted above. These agents are widely used as preservatives in foods and drugs and are clearly recognized as causes of severe contact dermatitis (65). There are three reports (66-68) of hypersensitivity reactions to parabens in the medical literature, a concern purported sensitivity to local anesthetics. Other studies (69-72), supported by clinical data, have shown the relevance of benzoates in adverse drug and food reactions such as eczema, asthma, urticaria and skin contact reactions. Balatsinou et al. (69) reported two cases of sensitivity to benzoates. The first patient (5 years old, male) had also shown adverse reactions (asthma, urticaria, angioedema) after drinking beverages such as "Coca-Cola" and orange-juice or eating mayonnaise and had several asthma attacks usually after taking drugs (syrups or suppositories) prescribed for colds. The second child presented a similar history of asthma worsened by oral formulation of anti-asthmatic or anti-inflammatory drugs usually prescribed for cold or flu and persistence or worsening of asthma after oral betamethasone.

In both cases the reactions were associated with ingestion of these additives. In fact, challenge with benzoate-containing formulations (paracetamol-syrup, flurbiprofen-syrup, erythromycin-suspension, amoxicillin-drops, ibuprofen-drops) induced asthma attacks, while the same molecules administered by benzoate free compounds (paracetamol-suppositories, flurbiprofen-suppositories, erythromycin-packets, amoxicillin-soluble tablets, ibuprofen-effervescent tablets) did not.

Sulfiting agents are used widely by the pharmaceutical industry as antioxidants. Some of the medications that contain sulfites are: bronchodilatator solutions, epinephrine, local anesthetics, corticosteroids, antibiotics, antiarrhythmics, analgesics, pressors, eye drops, solutions for total parentereral nutrition and dialysis, thorazine and others. Sulfites are also known to be present in some oral tablet formulations, but the amounts present are incapable of provoking reactions. When compared with the concentrations of sulfite in foods, most pharmaceuticals contain small amounts of sulfite (0.25% to 1%). Unfortunately, a small amount of sulfite may produce grave consequences in rare patients when inhaled directly into the tracheobronchial tree or injected parenterally (73). Twarog and Leung (74) have described a patient with asthma who experienced generalized pruritus, throat discomfort, and respiratory failure 2 minutes after receiving isoetharine by inhalation. Similar symptoms also developed after the intravenous administration of metoclopramide. Bisulfite was the only common chemical found in both agents.

Diagnostic approach

The diagnosis of an adverse reaction to food additives in children can be a true challenge for the clinician.

A *detailed medical history* is essential and a careful collection of the symptoms should be done. Because atopic children appear to be more likely to have adverse reactions to food additives, manifestations of atopy should be investigated.

Suspicion should be directed to food additives when there is an history of: 1- adverse reactions to several unrelated foods; 2- adverse reactions to a commercially prepared food but not when it is prepared at home; 3- aggravation of a pre-existing disease (i.e. AD) without explanation.

The next step is to rule out a "hidden" food allergen. The most common cause is unintentional contamination in the processing steps, but there are many ways for allergens to be hidden in food (75). One of the first record of hidden allergen in food allergy was reported in 1928 by Balyeat who described asthma symptoms in two peanut-allergic children after they had drunk milk from a cow fed on peanut plants (76).

A "Food and Symptoms Diary" can be useful in the diagnostic process. It helps to rule out a hidden food allergen and, checking the food labels, it can help to find out the common additive contained in suspected food that can be responsible of the patient's symptoms.

Diagnosis

Skin Prick Test (SPT) and *laboratory testing* detecting specific IgE can be used only for some natural

colorants (i.e. annatto, saffron, carmine, mannitol and vegetable gum).

The *Atopy Patch Test (APT)* can be used to find out delayed-type hypersensitivity reactions to foods and aeroallergen in atopic eczema (18). Catli et al. demonstrated that in a cohort of children with AE, positive APT results for Carmine were significantly higher in the AE than the control group suggesting a possible role of this natural colorant in AE. The authors conclude that the cost-effectiveness, safety, and practicability of the APT makes it a useful diagnostic tool for detecting delayed hypersensitivity to food additives in AE, especially with regard to late-phase clinical reactions (18). In a recent case report, APT was successfully used to find out an association between the consumption of foods containing Carmine and flares of AE in children with a history of AE (11).

The *DBPCFC* is considered the gold standard for the diagnosis of hypersensitivity to food and food additives (8, 10, 36).

Before performing the DBPCFC, adhesion to an additive-free diet (no more than 4 weeks) can be considered, to confirm the suspicion of an adverse reaction to food additives, if the patient's symptoms or manifestations improve (10, 36, 77). An example of an additive-free diet, according to EFSA regulations (5), is shown in Table 5.

The next step is an initial trial with multiple additives in order to reduce the number of challenge. If there is a positive reaction, the components of the challenge mixture should be tested separately, in order to identify the food additive responsible of the clinical manifestations (10, 36, 77). Protocols of oral challenge vary considerably among different studies (10, 78, 79) and to date there is not a consensus about the doses that should be used for the challenges.

Treatment

After performing the diagnostic tests, if a food additive is considered to be responsible of the clinical manifestations, the exclusion of the specific additive from the patient's diet is the effective treatment. The patients and the caregivers should be provided with all the names of the specific additive and should be aware about all the products (food, beverages, cosmetics and medicines) that might contain the culprit.

For patients with severe reactions (i.e. anaphylaxis) an appropriate action plan should be developed.

These patients must be provided with a medical identification tag and emergency medications (i.e.

Table 5. Example of an additive-free diet

Pasta	Any kind. *Avoid gluten-free and hypoproteic pasta.*
Meat	Beef, chicken, lamb, turkey, veal (fresh or frozen) *Avoid cold cuts and canned meat.*
Fish	Fresh or frozen fish. *Avoid processed fish and fishery products.*
Fruit and Vegetables	Fresh fruit and vegetable. *Avoid canned or bottled fruit and vegetables.*
Cheese	Mozzarella, Parmesan cheese.
Condiments	Honey, salt, pepper, sugar. *Avoid sauces, commercially prepared condiments.*
Beverages	Coffee, milk, tea, water. *Avoid alcoholic beverages, fruit juices, energy drinks, canned or bottled drinks.*

ephinefrine autoinjector) available all the time. To date, no studies have demonstrated a role for desensitization with food additives.

Conclusion

Additives are substances widely used in food industry, such as in cosmetics and medicines production processes.

A recent study conducted in USA, showed that the realistic level of daily exposure to food additives is deeply lower than ADI in children (80). This low exposure contributes to make adverse reactions to additives quite uncommon events and the diagnosis a real challenge for the clinician.

The diagnosis should be suspected in the presence of a suggestive clinical history. In this case the diagnostic process should be initiated. A IGE-mediated mechanism can be demonstrated only for a small number of additives in particular food dyes. The double-blind placebo controlled oral challenge after an exclusion diet represents the gold standard for diagnosis. If the suspicion is confirmed, an exclusion diet, without the culprit additive, is the only possible therapeutic approach.

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