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Adverse reactions to food additives in children: a retrospective study and a prospective survey

Short title: Adverse reactions to food additives in children

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Abstract

Background Allergic reactions to food additives are often suspected by families. The aim of this study was to describe oral food challenge (OFC) outcomes in a pediatric cohort with a suspected diagnosis of allergy to food additives (food dyes or sodium benzoate). **Methods** All patients who underwent an open OFC to carmine red, cochineal red, erythrosine, patent blue V, tartrazine, yellow sunset S, and/or sodium benzoate were included. A survey was sent to families after testing to evaluate whether the OFC results had altered feeding behaviors with food additives. **Results** Twenty-three patients were included. The main suspected food was candy ($n=11/23$; 48%). Only one OFC out of 45 was formally positive for the carmine and cochineal red. Subsequently, most OFCs were negative (44/45; 97.8%). Despite the negativity of the challenge, four families out of 14 reported occurrences of supposed allergic reactions to food additives and six out of 15 continued to completely avoid the additive of concern in their children's diet. **Conclusions** Allergies to food additives remain rare. Even if an IgE-mediated allergy was excluded with a negative OFC, families remained suspicious about ready-made products. Health professionals and parents should be reassured about the low risk of food dye intolerance or allergies.

Keywords: Carmine red; Cochineal red; Food dye; Hypersensitivity; Allergy; Children

1. Introduction

Food additives improve the preservation or the visual aspect of food and palatability. The safety of 40 food dyes has been reviewed by the European Food Safety Authority since 2009 in order to define acceptable daily intake (ADI) [1]. Actual consumption of the food additives is less than the ADI [2], excluding any possible toxic reaction. We can find several case reports on allergies to natural food dyes, which occur more frequently than allergies to synthetic food dyes [3,4]. However, while the most common natural food dye responsible for IgE-mediated reactions is carmine red (E120) [5,6], the prevalence of this allergy is in fact very low. Only a few studies have looked at the frequency of the allergic reaction to food dyes in the pediatric population [7,8], which suggests a lower incidence/prevalence than the IgE-mediated food allergy.

The aim of this work was to investigate whether oral food challenge (OFC) outcomes in a pediatric cohort supported a suspected diagnosis of an allergic reaction to food additives.

2. Methods

All the open OFCs to food dyes or sodium benzoate between January 2013 and April 2016, in the department of pediatric nutrition and gastroenterology at Trousseau Hospital-APHP in Paris, France, were analyzed retrospectively. There were no exclusion criteria. The food dyes and additives tested were determined according to the family interview and the analysis of the offending foods' labeling. A single dose of sodium benzoate (E211) (250 mg), tartrazine (E102), sunset yellow (E110), carmine red (E120), synthetic cochineal red (E124), erythrosine (E127), or patent blue V (E131) (2.5 mg each) was administered orally. The patient swallowed the capsule if he or she was able to do so, or the capsule was opened and mixed into a compote. The OFC was considered positive if an adverse reaction (cutaneous-

mucosal, respiratory, and/or digestive, with or without hemodynamic change) occurred within 3 h after ingestion, as per standard protocol.

The clinical reaction was scored according to the Astier score [9]: Astier 0: no symptoms; Astier 1: abdominal pain that resolved without requiring medical treatment, rhinoconjunctivitis, urticaria fewer than 10 papulae, rash (eczema onset); Astier 2: one organ involved, abdominal pain requiring treatment, generalized urticaria, nonlaryngeal angioedema, mild asthma (cough or fall of peak expiratory flow <20%); Astier 3: two organs involved; Astier 4; three organs involved or asthma requiring treatment or laryngeal edema or hypotension; Astier 5: cardiac and respiratory symptoms requiring hospitalization in intensive care. If the OFC was positive with a minor reaction (Astier 1), the protocol was to administer oral antihistamine (desloratadine) or simply wait for spontaneous resolution. In the case of a severe reaction with anaphylaxis (Astier ≥ 2), the treatment was an intramuscular epinephrine injection and monitoring at the hospital for at least 6 h. In case of an initial positive OFC carried out with a mixture of several dyes, we performed an individual OFC for each dye.

In the second part of the study between March and August 2017, a survey was sent to the parents to look for a possible recurrence of intolerance reactions to additives regardless of the outcome of the OFC, and to assess their behavior with dyes or food additives. They were contacted by mail, email, and/or phone with a maximum of three attempts over several weeks.

Continuous values were expressed as median, 25th and 75th percentiles, or range, or in raw values with the corresponding percentage in Microsoft Excel.

This study was approved by a national ethics review board (no. ID-RCB: 2017-A0169-44).

Parents received an information note about the right to refuse to participate.

3. Results

3.1 Description of the cohort

Twenty-three patients (14 girls, median age: 5 years at the time of symptoms) were suspected of being allergic to food dyes or preservatives. Allergological investigations possibly incriminated foods ($n=20$; 87%) and/or medicines ($n=7$; 30%). Candy was the main suspected food ($n=11$; 48%). In four patients, both food and drug vectors were found. Twenty-two patients described mucosal-cutaneous symptoms (localized or diffuse urticaria, pruritus, edema, or eczema), and one patient had diarrhea with paleness a few hours after ingestion of the suspected allergen.

3.2 OFC

Forty-five OFCs were performed, included 20 OFCs with a mixture of several food dyes. The most frequently tested allergens were carmine red ($n=20$) and synthetic cochineal red ($n=19$), followed by sodium benzoate ($n=13$), sunset yellow ($n=11$), erythrosine ($n=10$), and patent blue V ($n=9$). Native foods or drugs were also tested depending on the patient's history: sweets in various forms in five patients, amoxicillin in the form of syrup in two patients, ibuprofen syrup in one patient.

The median age at time of the OFC was 6.2 years (IQ25–75: 3.9–8.4 years).

Adverse reactions were noted in three OFCs (6.0%) in three patients (Table 1). The diagnosis of IgE-mediated allergy was only formally confirmed in one OFC out of 45 (2.2%). Patient A developed localized urticaria 60 min after ingestion of carmine and cochineal red (E120, E124), which resolved after treatment with oral antihistamine. All reactions were minor and are described in Table 1. For patient B, although the OFC to a mixture of E120, 124, and E127 was positive, the individual OFCs to each additive were negative. Patient C was allergic to ibuprofen and not to food dyes.

3.3 Follow-up survey

The survey was sent to families a median of 2.7 years after the OFC (range, 1.2–4.6 years). Fifteen families answered (65.2%), including the only true positive OFC (patient A). Despite a negative OFC, four out of 14 patients (28.6%) reported occurrence of minor reactions to the suspected allergenic food (Table 2).

Six out of the 15 families (40%) were still paying attention to the food or medicine given to their children (including patient A), especially by limiting the intake of candy in three patients, although no reaction had occurred.

4. Discussion

Among the 23 patients with suspected food allergy, only one patient had a formally confirmed allergy to the E120, E124 dye mixture determined by the OFC. Four other families reported recurrence of allergic reactions when their child consumed dyestuffs even though the OFCs were negative. Finally, 40% of the families who answered the survey (6/15) continued to monitor the presence of additives in their child's diet despite the negative OFC.

These results confirm the rarity of food dye allergy in a pediatric population of patients whose parents suspected these allergies. Prevalence of allergies to food dyes is low, ranging from 0.01 to 0.23%, reaching 2% in atopic children [7,8,10]. A placebo-controlled study showed that in cases of urticaria and/or angioedema that started after a meal containing sodium benzoate, an allergy to this preservative was often mentioned but was confirmed only in one out of 47 patients tested [11]. In another study, the diagnosis was confirmed in only 20 of 226 patients (8.8%) after a double-blind OFC in a population suspected of chronic rhinitis secondary to sodium benzoate allergy [12]. In a large Finnish study, 2926 patients suspected of food allergies underwent carmine red prick tests (E120). Skin tests were positive in 23 of 2926 patients (0.8%), but OFC confirmed clinical allergy in only five of them (0.2%) [13].

Even in selected children with a definite history of symptoms induced by artificial yellow colorings, additive allergy was finally diagnosed in only three out of 19 patients [14].

One child had a positive OFC when he simultaneously ingested several dyes, but a negative OFC with each dye tested separately. A synergism between the dyes could explain this surprising result. Indeed, dyes, in particular those of the azo family which can bind to serum human albumin (tartrazine, azorubine, Allura red, sunset yellow, yellow quinoline, patent blue V), could interact with each other in order to reach the target organs more easily than each isolated dye and thus cause allergic reactions [15].

We cannot exclude false-negative results for the four children whose OFCs did not confirm the allergy but who continued to have clinical reactions after ingestion of the additive. Indeed, the doses of additive or dye used during the OFCs reported in the literature [4] are sometimes much higher than those we defined according to the guidelines we used [16]. They range from 5 to 50 mg for tartrazine (E102) [8,12,14,17–21]; 5 to 50 mg for erythrosine (E127) [12,17,18]; 0.1 mg to 5 mg for carmine red (E120) [13]; 50 to 1000 mg for sodium benzoate (E211) [12,17,18,20]; and 5 mg for orange-yellow S (E110) [14,17], patent blue V (E131) and red cochineal (E124) [17]. It is therefore possible that some OFCs would have been positive if the doses used had been higher. It might therefore be preferable to define these doses by referring to the maximum consumptions described in the literature [1,2,22,23]. Dosages may be increased to 7.5 mg/kg for tartrazine, 1 mg/kg for sunset yellow, and 5 mg/kg for cochineal red.

Natural food dyes are the most often allergens responsible for immediate IgE-mediated allergic reactions. The only confirmed case in our cohort was allergic to carmine red/cochineal red. Indeed, carmine red is the best-known natural food dye. It is obtained from the spraying of dried, cochineal scales from cacti, used since ancient times for tinctures.

Several series of well-documented cases report anaphylactic reactions after ingestion of fruit yoghurt, colored ice cream, and in adults after consumption of Campari[®], mostly through an IgE-mediated mechanism [5,6,24,25]. The commercial carmine red prick tests were positive in 3.0% of a cohort presenting cutaneous or digestive symptoms linked to consumption of food or food additives (94/3164), but without clinical symptoms related to this food dye in 62% of them (58/94) [26]. Among these patients with clinical suspicion of carmine red allergy and positive prick tests, only five patients out of 23 were allergic according to positive single-blind OFC (facial and palmar urticaria; tingling of the lips and abdominal pain; tingling of the tongue; generalized isolated itch; localized pruritus) [13]. Prick tests performed in healthy controls were all negative ($n=20$) [6]. These various results seem to reflect a relatively frequent carmine red sensitization revealed by positive prick tests with no clinical correlation.

The two main limitations of the present study are its retrospective design and the absence of a double-blind food challenge. Although the double-blind placebo-controlled food challenge (DBFC) is the gold standard for confirming hypersensitivity, it is not performed routinely in children, and it requires capsules that young children are not always able to swallow [27]. Moreover, DBFC is more binding because the duration of the challenge could be longer, sometimes over 2 days, and could be responsible for indirect costs such as loss of working days for the parents [28].

This study was innovative in that it looked at feeding behaviors, regardless of the outcome of the OFC. Even if the OFCs were negative and without recurrence of symptoms, parents remained apprehensive about ready-made foods or drugs. To avoid these erroneous assumptions, the allergological history must carefully trace the chronology between the ingestion of the suspected food and the supposedly allergic reaction and look for the common denominator in food composition by studying the labeling [3,4,29]. We also note that viral urticaria is more frequent than allergy and that another cause of nonspecific localized rash

could be a histamine intolerance or a gustatory sweating such as in Frey syndrome [30], as in patient B. The skin prick test with commercial extract or native food, specific IgE if available, or the basophil activation test in specialized centers can help in the diagnostic procedure if an IgE-mediated food dye allergy is suspected, especially with natural food dye [3,23], but the OFC remains the only way to confirm an allergy [4].

5. Conclusion

These results and the literature support the rarity of hypersensitivity to food additives when this diagnosis is suspected by parents. Families remained suspicious about ready-made products even when the diagnosis of allergy was finally excluded with a negative OFC. Healthcare professionals and parents who could easily incriminate food additives or dyes should be reassured about the low risk of food dye allergy.

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Table 1: Details of positive oral food challenge (OFC)

Patient no. (age at the time of OFC)	History	Outcomes of oral food challenge (OFC)	Treatment
Patient A (6 years old)	Hen's egg IgE-mediated allergy Oral allergy syndrome with tomato Pruritus after ingestion of candy	Limited and localized urticaria 60 min after ingestion of E120, E124 (Astier Grade 1)	Antihistamine
Patient B (18 months old)	. Edema of the lower lip and tongue without dyspnea regressing with dexchlorpheniramine, 3 h after a meal in a fast food restaurant (chicken nuggets, fries, fruit compote, and pink lollipop) . Hen's egg allergy	. Positive OFC with a mixture of dyes (E120, E124, E127): limited and localized urticaria 45 min after ingestion (Astier Grade 1) . Negative OFC with E120, E124, E127 taken individually . Negative OFC with E110	Spontaneous resolution
Patient C (8 years old)	. Urticaria after ingestion of cherries . Face edema after oral ibuprofen . Urticaria and periocular edema when use of raspberry-scented shower gel	. Negative OFC with E120-E124 . Positive OFC with ibuprofen (cumulated dose 37 mg): limited and localized urticaria (Astier Grade 1)	Antihistamine

Table 2: Details of the survey for the patients who reported recurrence of reaction despite negative oral food challenge (OFC)

Patient no.	History	OFC (age at OFC)	Answer to the survey (age at the time of the survey)
Patient B	. Edema of the lower lip and tongue without dyspnea regressing with dexchlorpheniramine, 3 h after a meal in a fast food restaurant (chicken nuggets, fries, fruit compote, and pink lollipop) . Hen's egg allergy	Negative to E120, E124, E127, E110 (1.5 years)	The patient was still allergic to raw hen's egg. Parents preferred to avoid food dyes and cooked homemade food. (4.5 years)
Patient D	Urticaria after swallowing gummy candies	. Negative to sodium benzoate . Negative to a mixture with E110, E120, E124, E127, E131 (13 years)	Sensation of warmth and redness on the face without edema after consuming tomato, cheese or sweets with pungent sugars, without any criteria of severity. (18 years)
Patient E	Urticaria after taking particular forms of medications (ibuprofen syrup but not with tablets, paracetamol powder but not with syrup, betamethasone, and clavulanic acid plus amoxicillin), and after certain foods in which a particular ingredient could not be identified.	. Negative to sodium benzoate . Negative to amoxicillin syrup (6.8 years)	Local reactions after some eye drops. Parents believed that their child was still sensitive to some drug preservatives. (11 years)
Patient F	Itchy rash after meal with rice/dairy products/grapes; dimethicone oral gel for reflux; skin antiseptic (povidone-iodine); bandage	Negative to a mixture with E110, E120, E124, E131 (6.2 years)	Chronic urticaria (7.5 years)