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Reactions after natural and artificial food additives in urticaria: should we pretend they do not exist?

Reakcje na naturalne i sztuczne dodatki do żywności w pokrzywce. Czy powinniśmy udawać, że nie istnieją?

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ABSTRACT

Introduction: Hypersensitivity to food additives is still under investigation.
Aim: To evaluate the incidence of reactions to food additives and their clinical significance in urticaria patients and suspected hypersensitivity to them.
Material and methods: The study included patients hospitalized at the Department of Allergology and Pneumology of the Medical University of Gdansk in 2017–2019 with suspected hypersensitivity to food additives. The following substances were selected for the study: sodium metabisulfite, carmine, annatto, monosodium glutamate, sodium benzoate, and a mixture of azo dyes. A standardized questionnaire, skin prick tests, patch tests, and sIgE level evaluation for carmine were used in the diagnostic procedure. All the patients with positive skin testing, elevated sIgE level or suspected hypersensitivity for food additives were qualified for the single-blind placebo-controlled oral challenge.
Results: One hundred and ten patients were enrolled in the study. Out of 171 challenges carried out, 25 were positive in 22 subjects.
Conclusions: Food additives can exacerbate and induce hypersensitivity reactions in IgE- and non-IgE-dependent mechanisms.

KEY WORDS

food additives, carmine, sodium metabisulfite, annato, azo dyes, sodium benzoate, monosodium glutamate, inducible urticaria, chronic urticaria.

STRESZCZENIE

Wprowadzenie: Nadwrażliwość na dodatki do żywności jest wciąż przedmiotem badań.
Cel: Ocena częstości występowania reakcji na dodatki do żywności i ich klinicznego znaczenia u pacjentów z pokrzywką oraz podejrzeniem nadwrażliwości na nie.
Materiał i metody: Badaniem objęto pacjentów hospitalizowanych w Klinice Alergologii i Pneumonologii Gdańskiego Uniwersytetu Medycznego w latach 2017–2019 z podejrzeniem nadwrażliwości na dodatki do żywności. Do badań wybrano następujące substancje: pirosiarczyn sodu, karmin, annato, glutaminian sodu, benzoesan sodu oraz mieszaninę barwników azowych. W diagnostyce zastosowano standaryzowany kwestionariusz, punktowe

testy skórne, testy płatkowe oraz ocenę poziomu sIgE dla karminu. Wszyscy pacjenci z dodatnimi wynikami testów skórnych, podwyższonym poziomem sIgE lub podejrzeniem nadwrażliwości na wybrany dodatek do żywności zostali zakwalifikowani do pojedynczo zaślepionej doustnej prowokacji kontrolowanej placebo.
Wyniki: Do badania włączono 110 pacjentów. Przeprowadzono łącznie 171 prowokacji i uzyskano 25 wyników pozytywnych u 22 badanych.
Wnioski: Dodatki do żywności mogą nasilać i wywoływać reakcje nadwrażliwości w mechanizmach IgE-zależnych oraz IgE-niezależnych.

SŁOWA KLUCZOWE

dodatki do żywności, karmin, pirosiarczyn sodu, annato, barwniki azowe, benzoesan sodu, glutaminian sodu, pokrzywka indukowana, pokrzywka przewlekła.

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INTRODUCTION

Chronic urticaria (CU) is defined as the occurrence of wheals, angioedema, or both for more than 6 weeks [1]. The disease may affect 0.5% to 5% of the general population and significantly impairs quality of life [2]. The role of food additives in the pathogenesis of urticaria and angioedema (AE) is inconclusive, and the studies are inconsistent [3].

It is estimated that hypersensitivity reactions to food additives (FA) are relatively rare and affect less than 1% of the adult population; however, they are seen more often (1–7%) in atopic individuals [4, 5]. It is believed that the most common manifestation of hypersensitivity to food additives is urticaria [6, 7]. The EAACI recommendations also indicate a potentially beneficial effect of pseudoallergen-free and histamine-low diets in some patients with urticaria, despite the lack of proof in well-designed, double-blinded, placebo-controlled studies [1].

More than 330 food additives are authorized in the European Union, used as dyes, preservatives, antioxidants, sweeteners, emulsifiers, stabilizers, gelling agents, and thickeners. It is estimated that more than half of the food produced may contain at least one food additive, and over 10% of products may contain as many as five [8].

Many authors have stated that FA avoidance is not recommended in chronic urticaria [9].

This opinion, however, may be a simplification since allergic background or IgE-dependent anaphylactic reactions have been observed [10–13]. Therefore FA may act as allergens and generate IgE-mediated immune reactions, or they may act as pseudoallergens and cause non-IgE-mediated immune reactions [7, 9, 14, 15].

IgE-dependent reactions to dyes containing protein impurities, such as carmine [11] or annatto, have been reported [16]; however, hypersensitivity reactions to natural dyes are rarely diagnosed. Currently, there are no European and American recommendations for the diagnosis and management of hypersensitivity to carmine and annatto [17].

Artificial azo dyes and preservatives, such as monosodium glutamate and sodium benzoate, may also induce hypersensitivity reactions, but their immunological mechanism has not been confirmed [4, 6]. Sulfites are a group of food additives for which IgE and non-IgE reaction mechanisms have been described [18]. Their influence on asthma exacerbation in 3–10% of patients has been demonstrated [19]. Additionally, there are reports that 1/3 of sulfite hypersensitivity phenotypically appears as urticaria [20]. Hypersensitivity to FA should be suspected in individuals who report symptoms after consuming processed products, restaurant dishes, and artificially colored food such as sweets and drinks [4, 10].

AIM

The purpose of the research was to assess the incidence of food additive reactions and their clinical significance based on the placebo-controlled oral challenge in urticaria patients and suspected hypersensitivity to them.

MATERIAL AND METHODS

PATIENTS

The study included a group of patients (n = 110) with chronic urticaria, hospitalized at the Department of Al-

lergology and Pneumology of the Medical University of Gdansk in 2017–2019 with suspected hypersensitivity to FA. A standardized questionnaire for the selection of patients in the study was used. It contained demographic data, course of the urticaria to date, exacerbating factors in the patient's opinion, and efficacy of the previous treatment.

Before the hospitalization, patients did not take antihistamines or glucocorticoids for 7 and 30 days, respectively. Any special diet to follow was not recommended. Each patient had an intravenous line secured, blood pressure measured, and the patients with bronchial asthma underwent spirometry. Subjects with active urticaria within the last three days were not enrolled in the study.

The substances selected for the study included sodium metabisulfite (SMBS), carmine (CAR), annatto (ANN), monosodium glutamate (MSG), sodium benzoate (SB), and a mixture of azo dyes (AZO): tartrazine – E-102, Quinoline Yellow – E-104, Sunset Yellow – E-110, azorubine – E-122, Cochineal Red A – E-124, Allura Red AC – E-129. The methodology was adapted to each substance based on the existing knowledge of the tested food additives. Hypersensitivity was confirmed based on a single-blind, placebo-controlled oral challenge (OC).

Written informed consent to participate in the study was obtained from each participant. The study protocol was in line with the Helsinki Declaration on ethical principles, and the local bioethics committee approved it (NKBBN/546/2016-2017). Detailed characteristics of the group and methodology are included in previous publications describing the study results for a single food additive [21–25].

SKIN PRICK TESTS (SPT)

All the studied patients underwent skin prick tests with FA inducing potential IgE-mediated reactions, i.e., CAR, ANN, and SMBS. Saline and glycerol were used in a 1 : 1 ratio to prepare a 1% solution (10 mg/ml) of each studied substance. For annatto, a 1.2% solution was used. Positive and negative control was performed with histamine hydrochloride 10 mg/ml and saline (Allergopharma).

A wheal response diameter of a minimum of 3 mm with surrounding erythema larger than the negative control and representing the average of the two largest perpendicular dimensions was considered positive. Following other researchers [12], the test responses were measured at the 20th min (and additionally at the 30th min for CAR), and monitored for the next 5 h. The control group included 100 patients consulted at the outpatient Allergology Clinic without urticaria, who did not report any symptoms after FA ingestion and having negative skin prick tests.

PATCH TESTS (PT)

Patch tests for CAR and ANN on petroleum were prepared at 1% concentration, and for SB, and AZO commercially available tests were used (S-001, Mx-30, Chemotechnique Diagnostics, Vellinge, Sweden). Tests with SMBS were performed using both methods (including commercial test: S-011). Due to insufficient data on type IV hypersensitivity reactions, monosodium glutamate was not tested. Tests were placed in IQ-Ultra chambers (Chemotechnique Diagnostics) on the patients' backs and kept under occlusion for 48 h, then read at 48, 72, 96, and 168 h. The intensity of the reaction was scored according to the International Contact Dermatitis Research Group (ICDRG) rules [26]. Some readings were carried out on an outpatient basis.

SPECIFIC ANTIBODY LEVEL – F340

Serum IgE levels could be measured for carmine only (ImmunoCap, code f340, Thermo Fisher Scientific). The test was conducted in patients with suspected carmine hypersensitivity and a positive SPT. Given reports indicating that the low concentration of f340 was associated with allergic reactions [27], the value above 0.01 kU/l was considered positive in the study for research purposes.

SINGLE-BLINDED, PLACEBO-CONTROLLED ORAL CHALLENGE (OC)

To qualify for the oral challenge, a patient had to fulfill at least 1 of the following criteria:
1) positive SPT,
2) positive PT,
3) elevated f340 level,
4) suspected hypersensitivity for FA based on the detailed history and information from the questionnaire.

The scheme for OC was prepared for all mentioned food additives (SMBS, CAR, AZO, SB, ANN, MSG).

Table 1 presents the challenge protocols. The test was considered positive when urticaria or angioedema appeared within 24 h after verum administration but not after placebo. Adverse events were classified as objective (urticaria, angioedema, rhinitis, conjunctivitis, wheezing, coughing, vomiting, diarrhea, and collapse) or subjective symptoms. All the patients were under observation for at least 3 h after the last dose ingestion and were asked to contact the clinic to report a reaction (documented by a photograph).

The efficacy of the causative agent elimination after 12 and 24 months was assessed as the percentage frequency of urticaria or angioedema occurrence, excluding nutritional errors, when patients consumed the culprit food additive, followed by symptoms.

TABLE 1. Oral challenge protocols used in the study

Food additive	Placebo	Dose 1		Dose 2		Dose 3		Dose 4		Dose 5		Dose 6		Dose 7		Dose 8	
		Interval [min]	Dose [mg]	Interval [min]	Dose [mg]	Interval [min]	Dose [mg]	Interval [min]	Dose [mg]	Interval [min]	Dose [mg]	Interval [min]	Dose [mg]	Interval [min]	Dose [mg]	Interval [min]	Dose [mg]
Sodium metabisulfite	+	30	10	30	20	30	100	120	200								
Carmine	+	20	1*	20	2	20	5	60	10	60	20	60	50	60	100	60	150
Annato	+	20	1	20	2	20	5	60	10	60	20	60	50	60	100		
Azo dyes	+	120	Mix**	120													
Sodium benzoate	+	120	250	120	500												
Monosodium glutamate	+	120	500	120	1000												

*In the case of severe reaction in the past, 3 initial doses were added at the beginning (0.1; 0.2; 0.5 mg every 20 min); **content of one capsule with mixture of azo dyes was calculated as 10% of ADI (the acceptable daily intake) i.e.: tartrazine – 50 mg, Quinoline Yellow – 3.5 mg, Sunset Yellow – 7 mg, azorubine – 28 mg, Cochineal Red A – 4.9 mg, Allura Red AC – 49 mg.

STATISTICAL ANALYSIS

The significance of the association between food additive positive tests and other variables was analyzed with the χ^2 test/Fisher's exact test.

RESULTS

QUESTIONNAIRE

The patients' average age was 46 years (range: 20–76 years), where 69% were female. Isolated angioedema was reported by 16% of patients, isolated urticaria by 33%, and 51% suffered from both.

Treatment with antihistamines did not relieve symptoms in 42% of patients, while 36% reported partial improvement. Systemic reactions, defined as swelling of the throat or symptoms involving organs other than skin, were observed in 56% of the study group.

SKIN PRICK TESTS (SPT)

Positive carmine SPT (CAR SPT(+)) was observed in 17% of patients (n = 19). In all the groups, the wheal response size increased after 30 min compared to the 20 min evaluation. The largest weal size was observed after 2 h in 2 patients. Tongue swelling was found followed by SPT in 40 min in a 74-year-old patient with a positive history of carmine hypersensitivity. The positive SPT and f-340 results (6 mm and 0.99 kU/l, respectively) yielded carmine hypersensitivity diagnosis, and the challenge was not carried out. The analysis demonstrated that atopy (90% vs. 51%, $p < 0.011$) and systemic symptoms (84% vs. 51%, $p < 0.006$) were more frequent in the CAR SPT(+) group.

A positive skin prick test for sodium metabisulfite (SMBS) was observed in 20% of the patients (n = 22). In a 35-year-old female patient, the wheal response size scored in the 20th min increased from 3 to 6 mm after 3.5 h.

There was no positive SPT with annatto.

PATCH TESTS (PT)

The study revealed 18 positive patch tests in 16 patients: Mx-30 – 11, SMBS – 6, and BS – 1. In the SMBS patch test group, all six individuals had a history of both angioedema and urticaria, three of them suffered from throat edema, and 4 (67%) patients had a positive SMBS SPT ($p < 0.033$). The carmine patch tests were only doubtful in 6 patients, while annatto patch tests were negative.

PLACEBO-CONTROLLED ORAL CHALLENGE TEST (OC)

In total

Finally, a total of 171 challenges were carried out in 108 patients, among which 25 were positive in 22 subjects (SMBS: 13/64;

TABLE 2. Descriptions of patients with positive oral challenges

No.	F/M	Age	Asthma	Atopy	Years of disease	CAR SPT	CAR sIgE kU/l	CAR PT	CAR OC	SMBS SPT	SMBS PT	SMBS OC	ANN SPT	ANN PT	ANN OC	AZO PT	AZO OC	SB PT	SB OC	MSG OC	ASST	Exacerbating factors	U/AO	Systemic reactions	AH1 efficacy	Symptoms frequency after 12 months	Symptoms frequency after 24 months	Additional information from patients in follow up	Clinical diagnosis
1	M	24	–	+	0.5	+	0.04	–	NT	–	–	POS	–	–	NT	–	NT	–	NT	NEG	+	EX; F	U	+	+	100%	0%	Spontaneous remission after 24 moths	CSU exacerbated by SMBS?
2	F	67	+	+	12	–	0.41	–	NT	+	–	POS	–	–	NT	+	NT	+	POS	NT	–	F	U + AO (T)	+	+/–	20%	20%	Hypersensitivity to smells, exacerbation after different processed foods, strict diet used	CIndU exacerbated by SB hypersensitivity and SMBS allergy; MCS syndrom?; CAR sensitivity
3	F	44	+	–	17	–	0	–	NEG	–	–	POS	–	–	NT	+	NEG	–	NEG	NT	–	H; DP; EX; S; A; F	U + AO	+	+	100%	50%		CSU exacerbated by SMBS; Histamine intolerance
4	M	53	–	–	1	–	NT	–	NT	–	–	NT	–	–	NT	+	POS	–	NT	NT	–	I; S; A	U + AO	–	+	0%	0%	Remission after NSAIDs and azo dyes avoiding	CIndU induced by NSAIDs; AZO hypersensivity
5	F	64	–	–	10	–	0	–	NT	–	–	NT	–	–	NT	–	POS	–	NT	NT	–	DR	U + AO	–	–	0%	0%	Remission after azo dyes avoiding	CIndU induced by AZO hypersensivity
6	F	30	–	+	7	–	NT	–	NT	+	+	POS	–	–	NT	–	NT	–	NT	NT	+	SD; F	U + AO	–	+/–	30%	20%		CSU exacerbated by SMBS
7	F	31	–	+	4	+	0.02	–	POS	+	–	POS	–	–	NT	–	NT	–	NEG	NT	+	C; H; SD; VI; DP; EX; S; SC; F	U + AO (T)	+	+/–	25%	25%		CSU + CIndU induced by SMBS and CAR allergy
8	F	56	–	+	7	–	3.05	–	POS	–	–	NT	–	–	NT	–	NEG	–	NT	NT	NT	I; S; F	U	+	–	100%	100%	Migraine headaches, gluten-free diet	CSU + CIndU exacerbated by SMBS and CAR allergy
9	F	50	+	+	5	–	NT	–	NT	+	+	POS	–	–	NT	+	NEG	–	NT	NT	NT	SE; DR; F	U + AO (T)	+	+/–	100%	100%	Periodically diarrhea after meals	CSU exacerbated by SMBS?
10	F	60	–	+	6	–	NT	–	NT	–	–	POS	–	–	NT	–	NT	–	NT	NT	NT	EX; S; DR	AO (T)	+	–	0%	0%		CIndU induced by SMBS
11	M	21	–	+	0.5	–	0	–	NT	+	–	POS	–	–	NT	–	NT	–	NT	NT	NT	H; SE; F	U + AO	+	+	30%	30%	Probiotics helped in improvement	CSU exacerbated by SMBS

TABLE 2. Cont.

No.	F/M	Age	Asthma	Atopy	Years of disease	CAR SPT	CAR sIgE kU/l	CAR PT	CAR OC	SMBS SPT	SMBS PT	SMBS OC	ANN SPT	ANN PT	ANN OC	AZO PT	AZO OC	SB PT	SB OC	MSG OC	ASST	Exacerbating factors	U/AO	Systemic reactions	AH1 efficacy	Symptoms frequency after 12 months	Symptoms frequency after 24 months	Additional information from patients in follow up	Clinical diagnosis
12	F	72	–	+	2	–	0	–	NEG	+	–	POS	–	–	NT	+	NEG	–	NT	NT	–	C; SE; SW; S; F	U + AO	+	–	100%	100%	Hypersensitivity to cow's milk protein	CSU exacerbated by SMBS?
13	F	39	–	+	1.3	–	0	–	POS	+	–	POS	–	–	NT	–	NT	–	NT	NT	+	C; DP; EX; F	U	+	+/–	100%	25%		CSU+CindU induced by SMBS and CAR allergy
14	M	35	–	+	0.6	–	0	–	NEG	+	–	POS	–	–	NT	–	NT	–	NT	NT	+	S; F	U	+	–	100%	100%		CSU exacerbated by SMBS?
15	M	75	–	+	11	+	0.99	–	POS	–	–	NT	–	–	NT	–	NT	–	NT	NT	–	DR; F	AO (T)	+	+	10%	10%		CSU+CindU induced by CAR allergy
16	F	34	–	+	9	+	0.11	–	POS	–	–	NT	–	–	POS	–	NT	–	NT	NT	–	I; DR; F	U + AO (T)	+	–	25%	25%		CSU+CIndU induced by CAR and ANN
17	M	32	–	–	2.4	–	0	–	POS	+	–	NEG	–	–	NT	–	NT	–	NT	NEG	–	F	U + AO	–	+	10%	10%		CSU+CindU exacerbated by CAR
18	F	44	+	+	9.5	+	0.16	–	POS	–	–	NEG	–	–	NT	–	NT	–	NEG	NT	–	C; H; SE; AQ; SW; S; F	U	+	–	0%	0%	Remission of urticaria and eczema followed by carmine avoidance	CIndU and contact allergy induced by CAR allergy; histamine intolerance
19	M	39	–	–	2	–	NT	–	NT	–	–	POS	–	–	NT	–	NEG	–	NT	NT	–	DP; A; DR; F	U + AO	–	+	?	?	No follow up	CSU exacerbated by SMBS?
20	F	47	+	+	9	–	NT	–	NT	–	–	POS	–	–	NT	–	NT	–	NEG	NEG	+	DR; F	U + AO	–	–	40%	20%	Hypersensitivity to cow's milk protein	CSU exacerbated by SMBS
21	F	28	+	+	10	+	0.11	–	POS	–	–	NT	–	–	NT	–	NT	–	NT	NT	+	SW; I; F	U	+	+	20%	20%	Anaphylaxis after eating the cookie with CAR, elevated tryptase (15 µg / ml)	CIndU and anaphylaxis induced by CAR, histamine intolerance
22	F	26	–	–	4.5	–	0.02	–	POS	–	–	NEG	–	–	NT	–	NT	–	NT	NT	+	F	U + AO (T)	+	–	0%	0%		CIndU induced by CAR

F – female, M – male, CAR – carmine, SPT – skin prick test, PT – patch test, OC – oral challenge test, SMBS – sodium metabisulfite, ANN – annato, AZO – azo dyes mixture, SB – sodium benzoate, MSG – monosodium glutamate, ASST – autologous serum skin test, U – urticaria, AO –angioedema, T – throat edema, AH1 – antihistamines, NT – not tested, CSU – chronic spontaneous urticaria, CIndU – Chonic inducible urticaria, MCS – Multiple chemical sensitivity, NSAIDs – nonsteroidal anti–inflammatory drugs, POS – positive result, NEG – negative result, EX – excercise, F – food, H – heat, DP – delayed pressure, S – stress, A – alcohol, I – infection, SW – sweating, C – cold, SE – solar exposition, DR – drugs, SD – symptomatic dermographism, AQ – aqua, VI – vibration, SC – correlation with sex cycle.

CAR: 8/33; AZO: 2/39; SB: 1/18; ANN: 1/2; MSG: 0/15). Positive results for two tested FA were obtained in 4 patients: 2 – CAR and SMBS; 1 – CAR and ANN; 1 – SMBS and SB (Table 2).

In the patient group enrolled in the study based on positive skin tests or f340 level, ten scheduled challenges were not carried out in 9 patients (2 – SMBS; 8 – CAR). The reasons were refusal due to patients' fear, non-compliance (lack of time, absence on the day of the OC), and FEV_1 level below 70%.

Sodium metabisulfite, E-223 (SMBS)

A wide range of symptoms was observed (Table 3) during 13 positive OCs with SMBS. The reactions were noted at doses of 10, 20, 100, and 200 mg in 1, 3, 4, and 5 patients, respectively. The SMBS skin prick tests were positive in 62% of positive and 24% of negative challenge results ($p < 0.009$) [25].

Carmine, E-120 (CAR)

E-120 hypersensitivity was diagnosed in 9 patients. Eight carmine positive OC results were obtained. Skin reactions occurred after 2, 5, 50, 100, and 150 mg doses in 2, 2, 1, 1, and 2 patients, respectively. The smallest dose responsible for an angioedema reaction was one drop – approx. 0.5 mg was used during the skin test.

A positive SPT was found in 56%, while carmine sIgE > 0.1 kU/l was observed in 78% of patients with confirmed hypersensitivity to E-120. Compared to the rest of the studied individuals, all the patients in the carmine hypersensitivity group reported a history of facial reactions (100% vs. 82%, $p < 0.02$) and systemic symptoms (89% vs. 53%, $p < 0.02$) [23].

Azo dyes, E-102, E-104, E-110, E-122, E-124, E-129 (AZO)

Angioedema with urticaria following exposure to the azo dye mixture occurred in two subjects, accounting for 5% of the challenged patients.

In the first person, a 53-year-old patient with a history of hypersensitivity to acetylsalicylic acid, symptoms appeared after 6 h, and in the second, 64-year-old patient they appeared 90 min after verum administration. Two other people reported non-specific symptoms: in the first case, they were nausea and dizziness after 30 min, and in the second it was diarrhea after 5 h, which were not qualified as positive [22].

Sodium benzoate, E-219 (SB)

Among the 18 challenges with SB, one was found positive in a 67-year-old female patient with a positive patch test and a correlating history. The patient developed throat tightness, upper lip swelling, and abdominal pain 30 min after being administered 250 mg of sodium benzoate [24].

Annato, E-160-b (ANN)

Based on the information from the questionnaire, it was decided to make two provocations with annatto. One of them was a 34-year-old female patient with induced urticaria. Based on the analysis of the composition of the sun lotion and spray tanning agent used in the cosmetic studio, the presence of annatto in both products was determined. Upon administering 20 mg of ANN, slight erythema was observed in the cleavage area, and after its remission, the provocation was restarted, during which urticaria developed after the administration of 100 mg [21].

TABLE 3. Reactions that occurred during 25 positive oral challenges in 22 patients

Reactions	Sodium metabisulfite	Carmine	Azo dyes	Sodium benzoate	Annato
Urticaria	10	7	2		1
Angioedema	3	5	2	1	
Pruritus	3	2			
Weakness	2				
Rhinitis	2				
Conjunctivitis	1				
Shortness of breath*	1	1			
Tachycardia	1				
Headache	1				
Abdominal pain		1		1	

*Without obstruction in spirometry.

Monosodium glutamate, E-621 (MSG)

MSG challenge tests did not yield any positive reactions.

Skin reaction management

All the skin reactions described during the challenge significantly improved up to 3 h after administering the drugs. All patients in this group were given a double dose of antihistamines and, as needed, parenteral glucocorticosteroids. Two subjects required intramuscular adrenaline during the positive sodium metabisulfite challenge.

Assessment after 1 and 2 years from the study

The researchers contacted 21 out of 22 patients with positive challenge results after 12 and 24 months. Based on the positive challenge, elimination of the culprit food additive from the diet caused a reduction in symptoms in 67% of patients (14/21) after a year and 76% (16/21) after 2 years. At least 90% improvement was reported by 33% of patients (7/21) after 24 months. Diet mistakes with the culprit substance (intentional or not) caused a recurrence of similar reactions reported before hospitalization.

One patient developed anaphylaxis with generalized urticaria, abdominal pain, and weakness for the first time a few hours after consuming carmine cake. Five patients did not notice any improvement after eliminating the selected food additive, including one who reported spontaneous remission of urticaria.

DISCUSSION

In the discussed study, the authors diagnosed probable hypersensitivity to food additives in 20% (22/110) of the selected patients with urticaria.

The elimination of the food additive from the diet based on a positive oral challenge reduced the symptoms in 3/4 of the patients when maintaining the nutritional regimen in 24 months evaluation. Follow-up, when patients intentionally or not were exposed to the causative agent and had symptoms, confirmed the diagnosis.

Such a high percentage of hypersensitivity to food additives cannot be extrapolated to patients with chronic urticaria in general, as this investigation involved a selected group based on a detailed history, where over half of the studied patients reported systemic symptoms.

Many similar previous studies did not take into account additives of natural origin [9, 28–30]. Rajan *et al.* involved 100 patients in a single-, then double-blind test, concluding that the response rate to 11 additives (including E-102, E-110, MSG, SB, and potassium metabisulfite) in idiopathic urticaria was below 1% [9]. Di Lorenzo *et al.* found that among 876 patients with recurrent urticaria, OC with E-102, MSG, SB, SMBS, erythrosine, and hydroxybenzoate was positive in 1.7% of participants [28]. Hannuksela and Lahti obtained a positive reaction to SB twice in the same patient when they studied 44 patients with urticaria [29]. Nettis *et al.* observed a positive reaction to E-102 in 1 person in a double-blind test in a group of 102 patients [30].

In this study, there were two positive reactions with AZO, one with SB, and no positive reaction to MSG, which confirms that reactions to these artificial, frequently studied food additives are relatively rare.

Comparing individual studies with food additives is relatively difficult due to different protocols, patient selection, urticaria activity during the study, additive-free diet prior to challenge, use of antihistamines, positive challenge criteria, use of placebo, and blinding.

Moreover, different maximum doses of verum were used in the challenge schemes: for sulfites from a few to 200 mg [3, 9, 29, 31]; for SB 35 to 200 mg [3, 9, 29, 31, 32]; and for tartrazine from a few to 50 mg [9, 15, 30–32]. In the discussed study, rather high maximum doses of a given food additive were used, due to the possible dose-dependent nature of hypersensitivity, which could have resulted in a higher percentage of positive OCs.

The results of this study may highlight the underestimation of patients who react to natural dyes. The authors suggest that carmine SPT be performed at a concentration initially lower than 1% due to the observed anaphylactic reactions [33]. Perhaps CAR skin prick tests should be performed more frequently. Liippo *et al.* reported that they were positive in 3% of urticaria patients. These researchers also found that the carmine challenge test was positive in 22% of patients with positive SPT, compared to 36% in the current study. The Finnish authors only challenged patients with positive CAR SPT results [34], while elevated serum IgE level (f340) was the inclusion marker in the current study. The total carmine dose in the challenge protocol was also different: 5 mg vs. 338 mg (but below ADI – the acceptable daily consumption, i.e., 5 mg/kg bw/day).

There is evidence that patients with carmine allergy may be sensitized by occupational contact or through the skin in cosmetics [35]. It is important to note that the frequency of sensitization may correlate with the amount of exposure to a given allergen via skin. Skin sensitization may explain the more frequent anaphylaxis reports in Japan after consuming imported carmine-containing products. There are no restrictions on adding carmine to cosmetics; however, carmine is not allowed in food in this country [13]. Currently, using natural additives in food and cosmetics is increasing instead of artificial ones, which may contribute to a greater

frequency of hypersensitivity reactions to natural products in the future.

The mechanism of the non-IgE-dependent action of food additives is unknown. Murdoch *et al.* observed an increase of serum histamine after tartrazine consumption in healthy subjects [36]. In an *in vitro* study, Matsuo *et al.* found that basophils incubated with selected food additives released histamine into the blood through increased Syk kinase activation, but only when specific anti-IgE antibodies were added. These authors reported that tartrazine, sunset yellow, aspirin, and the NSAIDs without anti-IgE activation increased histamine levels slightly, below 5%. Then basophil activation by the addition of specific anti-IgE antibodies caused an increase in histamine release by 30–40%, and the addition of tartrazine, sodium benzoate, and aspirin caused an additional dose-dependent significant increase in histamine release [37]. The study suggested that patients with chronic urticaria might react to food additives in a non-IgE-dependent mechanism while such reactions may not be observed during remission of the disease.

The present study confirmed that many subtypes of urticaria could coexist in the same patient in practice [1]. Patients with a positive challenge to food additives, similarly to the entire study group [38], indicated many physical and non-physical factors exacerbating the course of urticaria, which makes it challenging to classify only one urticaria subtype in a given patient.

Identification of underlying causes such as allergy or infectious diseases allows the causative management in urticaria. However, in practice, determining exacerbating factors is important for patients for better disease control. Still careful medical history and blinded, placebo-controlled challenge tests are crucial in urticaria diagnostics.

CONCLUSIONS

Food additives can exacerbate and induce hypersensitivity reactions in the IgE and non-IgE-dependent mechanisms. Hypersensitivity to food additives, especially allergic reactions to natural dyes and sodium metabisulfite, seems to be underdiagnosed and requires further research.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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