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Food-Additive-Induced Urticaria: A Survey of 838 Patients with Recurrent Chronic Idiopathic Urticaria

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Key Words
Diet · Double-blind placebo-controlled challenge · Food additives · Urticaria

Abstract

Background: Recurrent chronic idiopathic urticaria (RCIU) is a common skin condition that affects 0.1–3% of the population in the USA and Europe and accounts for nearly 75% of all 'ordinary' chronic urticaria (CU) cases. ***Methods:*** We studied 838 consecutive patients with RCIU referred to hospital between 1998 and 2003. Patients with known causes of CU were excluded. Clinical history, physical examination, and symptom diaries were evaluated during two periods, a diet-free period (1 week) and a food-additive-free diet (FAFD) period (4 weeks), respectively, and two double-blind placebo-controlled (DBPC) challenges of six food additives were administered. The first DBPC challenge included a mixture of the six food additives ($DBPC_{mixed}$) given to all patients. The second DBPC challenge comprised the single food additives, administered at increasing doses ($DBPC_{single}$) to patients with a positive $DBPC_{mixed}$ test and 105 patients with a negative $DBPC_{mixed}$ test, as a control. ***Results:*** The $DBPC_{mixed}$ challenge was positive in 116 patients. None of the 105 control patients had a positive $DBPC_{single}$ test. Only 31 $DBPC_{single}$ tests were positive in patients with positive $DBPC_{mixed}$ challenge. Twenty-four of the 116 patients showing a positive $DBPC_{mixed}$ challenge also had a positive $DBPC_{single}$ result. ***Conclusions:*** Our results confirmed that food additive hypersensitivity reactions occurred in few RCIU patients using $DBPC_{single}$ challenge. The combination of the results of FAFD and $DBPC_{mixed}$ challenge seems to be of considerable practical interest for allergists, internists and dermatologists, rather than the data of clinical history and the results of $DBPC_{single}$ challenge, in patients with RCIU.

Introduction

Urticaria is a common skin reaction that occurs in approximately 15–20% of the general population [1–4]. It is characterized by transient, erythematous, raised skin lesions that are usually intensely pruritic. By definition,

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Table 1. Individual sign and symptom score system

Score	Pruritus	No. of hives	Size of the largest hive (cm)	Angioedema
0	none	none	none	none
1	mild (minimal awareness, easily tolerated)	1–6	<1.25	located in one part of the body, >2 cm in diameter
2	moderate (definite awareness, bothersome but tolerable)	7–12	1.25–2.5	located in two parts of the body, each <10 cm in diameter
3	severe (difficult to tolerate)	>12	>2.5	located in three parts of the body or diffuse, >10 cm in diameter

urticaria of <6 weeks duration is arbitrarily considered 'acute', whereas urticaria recurring >6 weeks is referred to as 'chronic'. Since a strict distinction between different types of chronic urticaria (CU) is difficult, the term recurrent/chronic idiopathic urticaria (RCIU) was used in this study [1–6].

Generally, 70–80% of the patients with 'ordinary' CU do not have a well-described cause, and 0.1–3% of the US and European population are affected [4]. Acute urticaria is much more likely to be caused by food allergy than CU. However, there is a subgroup of patients with RCIU with food-additive-evoked urticaria [7–22].

Food additives are a heterogeneous group of substances, including preservatives, such as antimicrobials and antioxidants, dyes, colorants, emulsifiers, stabilizers and sweeteners, which are used in several foods, either singly or in combination [23–25]. The reactions to food additives are given various terms, e.g. 'idiosyncrasy', 'intolerance' and 'pseudoallergy', because they are not based on a sensitization of the immune system. Recently, the European Academy of Allergy and Clinical Immunology used the term nonallergic 'hypersensitivity' for these reactions [6]. However, in this study we use the term 'hypersensitivity to food additives' (HFA).

The diagnostic tools available to determine whether a food ingredient or a food additive plays a role in the patient's urticaria include clinical history, physical examination, symptom diaries, elimination diets and double-blind placebo-controlled (DBPC) challenges [1–6, 26–29]. However, many of these HFA studies are inadequately controlled, and results have not been confirmed [30–32].

The aim of this study was to determine the prevalence of HFA among subjects with RCIU, using two DBPC challenges: the first with a mixture of six additives and the second using the six additives singly.

Patients and Methods

Patients

A total of 838 consecutive patients with RCIU (547 females and 391 males), with ages ranging between 16 and 74 years (mean age 38.1 ± 15.3 years), were referred to the Outpatient Clinics of the University Hospitals in Verona and in Palermo (Italy). RCIU was defined as the presence of urticarial lesions recurring >6 weeks, in which more than three episodes occurred per week, without any known secondary causes [1–5]. The presence of urticarial skin lesions, with or without angioedema, was clinically confirmed in all patients.

The study comprised all patients who consulted our Allergy Outpatient Clinics of the University Hospitals in Verona and in Palermo (Italy) between January 1995 and December 2003. All the patients had been referred by a general practitioner to have the cause of their urticaria verified. Patients with known cause were excluded from the study. As no alternative test for HFA exists, authorization of the food additive provocation test study is not required according to our institutional policy and the ethical committees of our institutions. However, written informed consent to the test and review of his/her records was obtained from every patient, in compliance with our institutional policy. Patients with physical urticaria, with positive skin test to autologous serum, or with appearance of urticaria after administration of acetylsalicylic acid (ASA) or non-steroidal anti-inflammatory drugs (NSAIDs) were excluded from the study.

All patients underwent a standardized evaluation at the two clinics including a standardized questionnaire. In particular, patients were questioned concerning any food or drinks which they associated with attacks of urticaria, including ready-made products and preserved foods. Urticaria was defined as mild, moderate or severe, based on the symptoms reported in table 1 [33, 34].

A daily diary card was given to record the symptoms for 1 week. Patients assessed disease activity using a scoring system for RCIU symptoms and signs that were evaluated using 4-point scales (0–3) for pruritus, number of hives, size of largest hive and presence of angioedema (table 1) [32, 33].

One week later, the patients started a food-additive-free diet (FAFD) [3, 13, 18–22]. Table 2 presents the foods excluded from the 4-week diet [19, 20, 35]. After FAFD (4 weeks later), the daily diary cards were checked again to assess whether any patients had experienced reduced urticaria symptoms during the FAFD.

Food-Additive Challenges

We performed two DBPC challenges. We use the abbreviations $DBPC_{mixed}$ for the first challenge and $DBPC_{single}$ for the second. Food additives and placebo were in gelatin capsules and had the same appearance for both the $DBPC_{mixed}$ and the $DBPC_{single}$ challenges. The patients, the physician and the ward assistants were all blinded to the contents of the challenges. The food additive challenge was performed under the supervision of the physician. Bronchodilators, adrenaline and resuscitation equipment were available at all times for the treatment of any acute reaction, if any were to occur. Challenges were administered during the morning hours. The substances and the placebos were given in randomized sequence, without sham challenge with placebo. Both subjective symptoms (pruritus) and objective signs (number and size of hives, angioedema) were carefully recorded after each dose. The results of the challenge were considered 'positive' when the patients developed either worse objective signs or a relapse of hives and angioedema with pruritus after each capsule. The results were considered 'negative' when the patients had only subjective changes of pruritus. In this study, the scale reported in table 1 for the evaluation of subjective and objective symptoms of the challenges was also used. The objective symptoms were evaluated by the physician.

$DBPC_{mixed}$ Challenge

After FAFD, all patients – whether they had improved or not – performed the $DBPC_{mixed}$ challenge. Each capsule contained the second dose of all the additives subsequently used singly for the $DBPC_{single}$ challenge, or placebo (talc; table 3). The pharmacist prepared a specific set with two capsules, one with the mix of six food additives and the other with talc. The time of the administration between the first (mix of food additives or talc) and the second capsule (mix of food additives or talc) was an interval of 2 h, if no objective symptoms had developed after the first capsule. On the contrary, if symptoms or onset of new hives or angioedema appeared 2 h after the first capsule, the second capsule was administered after a week. The order of randomization has been obtained with a specific software.

$DBPC_{single}$ Challenge

The $DBPC_{single}$ challenges were performed in all patients with positive $DBPC_{mixed}$ challenge. As controls, we performed the $DBPC_{single}$ test also in 105 patients with negative $DBPC_{mixed}$ test: in 21 patients with a food-related clinical history and improvement of symptoms during FAFD, in 21 patients with a food-related clinical history but without improvement of symptoms during FAFD, in 21 patients without food-related clinical history but with improvement of symptoms during FAFD, and finally in 42 patients without food-related clinical history and without improvement of the symptoms during FAFD.

For each of the six chemicals, the pharmacist prepared a specific set with three doses of food additives and three placebo capsules (table 3), in randomized sequence (three capsules of food additives or three capsules of placebo, i.e. food additive or placebo or vice versa). One sequence of food additive at a time was used for the challenge and tested for at least a 1-week interval with another food additive sequence. For every sequence, the subsequent capsule was given after a 2-hour interval, if no objective symptoms had developed during the previous administration. The same method of evaluation reported above ($DBPC_{mixed}$) was used for the $DBPC_{single}$ challenge.

Since the patients were all affected by RCIU, they could ingest their usual antihistamine therapy as needed for the whole period of the study.

Table 2. Food-additive-rich food excluded from the 4-week FAFD

Breakfast	Muesli, dried apricots (containing sulfites), yoghurt, margarine, honey and jam (containing preservatives)
Lunch and dinner	Instant broth (containing glutamate), tinned spaghetti in tomato sauce (containing preservatives), potato salad and fish salad (containing benzoic acid), matured cheese and ham (containing preservatives), burgers, olives, seasoning: paprika, thyme, oregano, pepper, nutmeg, oil, vinegar, garlic, onion, fruit jelly (containing coloring agents), apple, blueberries/strawberries (fresh or frozen; containing benzoic acid)
Drink	Coffee, tea, chocolate bar, fizzy drinks (containing benzoic acid and coloring agents)

Table 3. Doses used for DBPC challenges

Substances under investigation	Dose, mg				
	first	second	third	lowest	higher
Tartrazine (E102)	10	10	20	10	40
Erythrosin (E127)	50	50	100	50	200
Monosodium benzoate (E211)	50	50	100	50	200
p-Hydroxybenzoate (E218)	50	50	100	50	200
Sodium metabisulfite (E223)	5	5	10	5	20
Monosodium glutamate (E620)	100	100	200	100	400

A mixture of the second dose of all additives was used in a single capsule for the $DBPC_{mixed}$ challenge.

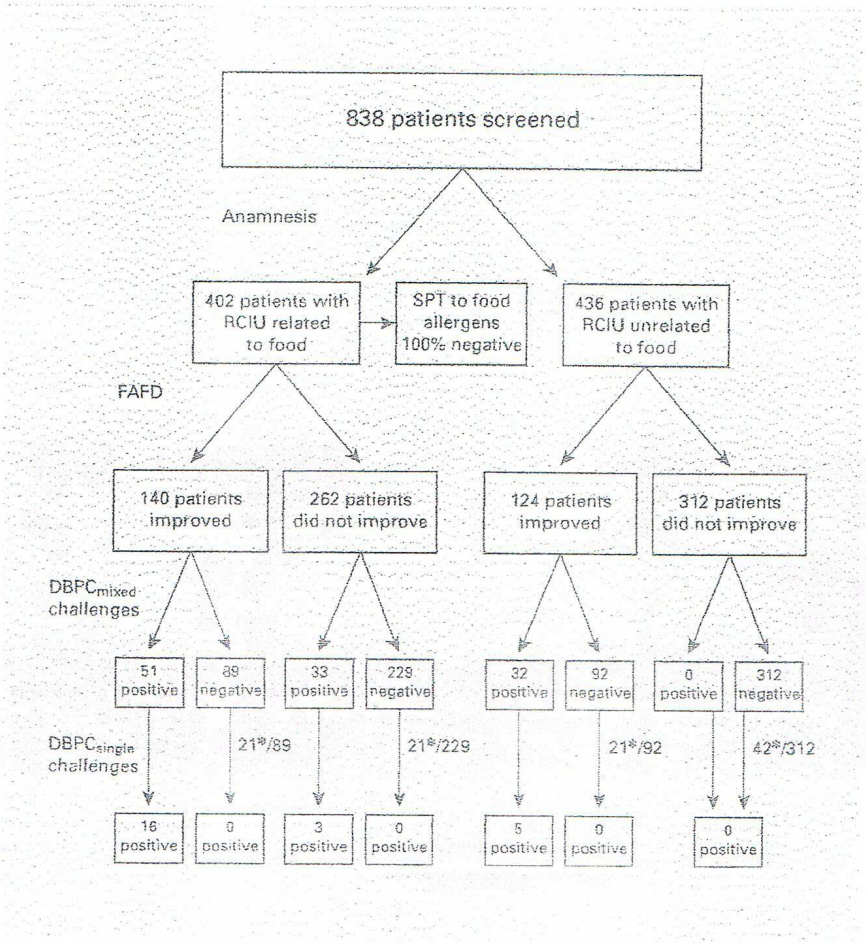

Fig. 1. The study population. Asterisk denotes patients with negative $DBPC_{mixed}$ challenge that performed the $DBPC_{single}$ challenge as control (105 patients in total). SPT = Skin prick test.

Statistical Analysis

For each patient, the mean of the daily score of symptoms of urticaria during the pre-DBPC period was calculated from the mean (95% confidence interval, CI) of the means of individual total symptom scores. Analysis of covariance was used to account for any effect, including diet response, to the antihistamines used as rescue medication during the entire period of the investigation. Adjusted values were subsequently averaged per patient over the entire observation period. The averages per patient were examined using a 'mixed effects' ANOVA model with the response to diet (as fixed effect) as main factors, and the centers as random effect; F values were calculated using the mean squares of the interaction 'centers × periods' as error term. Differences between means were evaluated by Bonferroni's multiple range test (set at 95% CI). The other data were expressed as means ± SD. We used the χ^2 test to compare the different percentages. Comparisons are only denoted if they are significant ($p < 0.05$, two tailed). The exact one-side binomial CI was determined. All analyses were performed using the SYSTAT 10 software package (SPSS).

Results

Patient Characteristics

Six hundred and fifty-six (78.3%) patients had only urticaria and 182 (21.7%) patients had urticaria and angioedema; no patient had only angioedema. One hundred and thirty-nine patients (16.6%) were dissatisfied with the use of antihistamine treatment only. The results of the study are summarized in figure 1.

Clinical Histories

Four hundred and two patients (48%) reported an indicative history, which suggested food and/or drinks as factors inducing their urticaria. Fifty percent of these patients also indicated ready-made products and preserved food as possible factors. Fruit- and vegetable-based products were mentioned, especially fruit juices, cordials and tonic water. The skin prick test to food allergens was per-

formed in these patients (n = 402) and was negative in all cases. It is important to underline that the patients denoted food or drinks, not food additives.

Using the clinical history only, as gold standard, we found that, with 95% confidence limits, HFA in patients with RCIU occurs somewhere between 39 and 46% of the CU population.

FAFD Period

Two hundred and sixty-four out of the 838 patients had improvements in their symptoms while on FAFD (31%), whereas 574 patients did not improve. Using the FAFD only, as gold standard, we found that, with 95% confidence limits, HFA in patients with CU occurred somewhere between 28 and 34% of the CU population.

In particular, 140 (53.0%) out of the 264 patients who improved during the diet period reported a clinical history suggesting food and drinks as causes of their urticaria, whereas 124 (47.0%) did not report this. Of the 574 patients who did not show improvement with FAFD, 444 discontinued the diet after 15 days because of low compliance.

In the group of patients who reported an improvement (264 individuals), the mean of the total urticarial symptoms score before FAFD (9.4, 95% CI 9.1–9.7) was significantly higher than after the diet (2.7, 95% CI 2.4–3.0), with a mean difference of –6.6 (95% CI –7.0 to –6.1, $p < 0.01$). However, no patients presented complete remission of urticaria. In the non-affected group (574 individuals), we evaluated only 130 patients (see above), and no significant change in the urticarial symptom score, including deterioration of symptoms, was observed: the mean value was 7.4 before FADF (95% CI 7.4–7.5) and 7.3 after the diet (95% CI 7.4–7.2), with a mean difference of –0.1 (95% CI –0.2 to 0.007, p = nonsignificant).

$DBPC_{mixed}$ Challenge

One hundred and sixteen patients (13.8%) had a positive challenge result. Using $DBPC_{mixed}$ challenge only, as gold standard, we found that, with 95% confidence limits, HFA in patients with CU occurred somewhere between 11.5 and 16.3% of the CU population. However, no patients without a clinical history related to food and without improvement in symptoms during the period of FAFD presented a positive $DBPC_{mixed}$ challenge.

$DBPC_{single}$ Challenge

None of the 105 control patients had a positive $DBPC_{single}$. There were 2,406 (98.7%) negative $DBPC_{single}$ challenges in patients with positive $DBPC_{mixed}$ challenge. Only 31 $DBPC_{single}$ challengen tests were positive. Twenty-four out of the 116 patients (20.7%) who had a positive $DBPC_{mixed}$ challenge also had a positive $DBPC_{single}$ result. In 18 patients, the $DBPC_{single}$ challenge was positive to one of the six food additives tested, in 5 patients to two food additives and in 1 patient to three food additives. Using only $DBPC_{single}$ results, as gold standard, and considering that no patients with negative $DBPC_{mixed}$ challenge presented a positive $DBPC_{single}$ challenge, with 95% confidence limits, HFA in patients with CU occurred somewhere between 1.8 and 4.2% of the CU population studied. Instead, considering the entire procedure (clinical history, clinical response to FAFD, and positive $DBPC_{mixed}$ and $DBPC_{single}$ challenges), we were able to demonstrate the etiologic role of food additives only in 16 patients (95% CI 1–3%). To rule out that the results of positive $DBPC_{mixed}$ challenges and negative $DBPC_{single}$ challenges could be false-positive results, we repeated in some patients (35/92), who gave their consent, a new $DBPC_{mixed}$ challenge, which confirmed the previous results, resulting positive. On the basis of these results, we believe that food additives are apparently only triggers or aggravating factors and that they possibly exert a synergistic effect among them or with food to which they were added.

In patients who had a positive $DBPC_{single}$ challenge, the food additives inducing subjective and objective symptoms of urticaria are reported in table 4. All relapses and deteriorations of urticaria were completely reversed by H_1-antihistamines plus prednisolone.

Discussion

The major result of this study is that confirmed HFA reactions occurred in only a few patients with RCIU, using $DBPC_{single}$ challenge [30]. Our results indicate that HFA is somewhere between 1.0 and 3.0% in the chronic urticaria population. Nevertheless, we have demonstrated that RCIU evoked by food additives, both with $DBPC_{mixed}$ (between 5.0 and 10.0%) and with $DBPC_{single}$ challenges (between 0.3 and 1.0%), can also be present in patients without a clinical history of urticaria related to food. Both $DBPC_{mixed}$ and $DBPC_{single}$ challenges were positive in patients without a clinical history related to food and without improvement during the period of the FAFD. However, routine $DBPC_{mixed}$ challenge testing of such patients could be justified as a form of screening in patients with RCIU presenting a clinical history related to food and improvement of urticaria during the FAFD

Table 4. Results of $DBPC_{single}$ challenges in the patients with positive $DBPC_{mixed}$ challenges (n = 116) and in 105 patients as a control

Patients	Placebo			E102			E127			E211			E218			E223			E620		
	I	II	III	I	II	III	I	II	III	I	II	III	I	II	III	I	II	III	I	II	III
1	–	–	–	–	+	NA	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
2	–	–	–	+	NA	NA	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
3	–	–	–	–	+	NA	–	–	–	–	–	–	–	–	–	–	+	NA	–	–	–
4	–	–	–	–	–	–	–	+	NA	–	–	–	–	–	–	–	–	–	–	–	–
5	–	–	–	–	–	–	–	+	NA	–	–	–	–	–	–	–	–	–	–	–	–
6	–	–	–	–	–	–	–	+	NA	–	–	–	–	–	–	–	–	–	–	–	–
7	–	–	–	–	–	–	–	+	NA	–	–	–	–	–	–	–	–	–	–	–	–
8	–	–	–	–	–	–	–	–	+	–	+	NA	–	–	–	–	–	–	–	–	–
9	–	–	–	–	–	–	+	NA	NA	–	–	–	–	–	–	–	+	NA	–	–	+
10	–	–	–	–	–	–	–	–	–	–	+	NA	–	–	–	–	–	–	–	–	–
11	–	–	–	–	–	–	–	–	–	–	+	NA	–	–	–	–	–	–	–	–	–
12	–	–	–	–	–	–	–	–	–	–	+	NA	–	–	–	–	–	–	–	–	–
13	–	–	–	–	–	–	–	–	–	–	+	NA	–	–	–	–	–	–	–	–	–
14	–	–	–	–	–	–	–	–	–	–	+	NA	–	–	–	–	–	–	–	–	–
15	–	–	–	–	–	–	–	–	–	+	NA	NA	–	–	–	–	+	NA	–	–	–
16	–	–	–	–	–	–	–	–	–	–	+	NA	–	–	+	–	–	–	–	–	–
17	–	–	–	–	–	–	–	–	–	–	–	–	–	+	NA	–	–	–	–	–	–
18	–	–	–	–	–	–	–	–	–	–	–	–	–	+	NA	–	–	–	–	–	–
19	–	–	–	–	–	–	–	–	–	–	–	–	–	+	NA	–	–	–	–	–	–
20	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	+	NA	–	–	–
21	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	+	NA	–	–	–
22	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	+	NA	–	–	–
23	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	+	NA	–	–	+
24	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	+	NA
25–129[a]	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Total tests	221	221	221	221	220	218	221	220	216	221	220	213	221	221	218	221	221	214	221	221	220
Total positive reactions	0	0	0	1	2	0	1	4	1	1	7	0	0	3	1	0	7	0	0	1	2
%	0	0	0	0.4	0.9	0	0.4	1.8	0.4	0.4	3.1	0	0	1.3	0.4	0	3.1	0	0	0.4	0.9

NA = Not applicable; + = positive reaction; – = negative reaction; I–III = doses; E102 = tartrazine; E127 = erythrosin; E211 = monosodium benzoate; E218 = *p*-hydroxybenzoate; E223 = sodium metabisulfite; E620 = monosodium glutamate.

[a] Control subjects with negative $DBPC_{mixed}$ challenge.

period. The cost of the entire diagnostic procedure is only €3 per patient.

In contrast to genuine IgE-mediated allergy, with typical symptoms closely related to the ingestion of sensitizing foods, HFA is more difficult to diagnose. In vivo and in vitro tests are unreliable, and diagnosis is consequently based on oral provocation [27–29]. For these reasons, there has been a gradual falling away of medical interest in HFA as a cause of urticaria, counterbalancing increasing public awareness [36–38].

It has been suggested that when the clinical history is related to additives contained in food products, a period of FAFD might be of diagnostic help. If the urticaria symptoms disappear completely during the FAFD period, a challenge test with an individual additive is the last step in this diagnostic approach [1–5, 32].

Our study was based on the above principle, but considering the results of the clinical history, the FADF period and the $DBPC_{single}$ challenges, in our daily clinical practice we introduced $DBPC_{mixed}$ challenges in the management of RCIU.

Food-additive-related symptoms detected on the basis of case history data were not very informative [39]. In their clinical histories, the patients (n = 402) indicated food or drinks, but not food additives; they also reported symptoms without the intake of such food or drinks. On the other hand, in patients (n = 436) who did not report any evident relationship between specific foods or drinks and their symptoms, urticaria symptoms seemed to occur spontaneously or worsened after a meal. In both cases, an urticaria related to food additives may be hypothesized. As the presence of food additives is not always apparent

in food, the relationship between the ingestion of the additive and the symptoms of urticaria is also obvious, either for the physician or for the patient.

Therefore, whether the clinical history of RCIU is related to food or drinks or not, the clinical pattern of urticaria related to HFA is similar to any other 'ordinary' CU. The main reason for this is that food additives may be present in the daily diet and presumably act as chronic potentiators of continuing urticaria [35]. This would explain the improvement in urticaria during FAFD both in patients with (n = 140) and without (n = 124) clinical histories related to food.

The discrepancies between the results of the FAFD, $DBPC_{mixed}$ and $DBPC_{single}$ challenges might be related to the combined or synergistic effects of food additives with each other or with other food compounds. In the light of this hypothesis, the formation of natural food additives, e.g. aromatic compounds from tomatoes, for example, has been described [40].

Our study is based on a small number of food additives compared to the vast number of additives used in food processing (with an estimated range between 2,000 and 20,000). The food additives were chosen on the basis of the data of previous studies and on our own previous experience [7–22]. However, our results suggest that the food additives are only triggers or aggravating factors in RCIU. In fact, in 35 patients with positive $DBPC_{mixed}$ challenge, the challenges were twice positive in the same patients that were negative to $DBPC_{single}$ challenge. On the other hand, during a normal meal, everyone is exposed to more than one food additive. During the period of FAFD, no patients with positive $DBPC_{mixed}$ or $DBPC_{single}$ challenges presented complete disappearance of urticaria. Our results confirm that FAFD is not even a therapeutic choice in patients affected by RCIU [1–5, 32]. These results are similar to those obtained from challenges to ASA or NSAIDs in patients affected by RCIU, with or without a history suggesting a causal role of anti-inflammatory drugs [1–5]. In other words, the exclusion of ASA and/or NSAIDs, in patients with RCIU and ASA and/or NSAID hypersensitivity, does not obligatorily lead to remission of urticaria [1–5]. Clinically, this comparison is important also for the choice of therapy in these patients, considering that, in our clinical experience, particular subgroups of patients affected by RCIU with ASA or HFA do not all respond to H_1-antihistamines [22]. In our previous study, we successfully treated patients with hypersensitivity to ASA and/or HFA with leukotriene receptor antagonists (i.e. montelukast) [22]. The use of leukotriene receptor antagonists has been proposed in patients who respond poorly to antihistamines [41, 42]. On the contrary, in patients with no known cause of their urticaria ('very chronic idiopathic urticaria'), the use of leukotriene receptor antagonists combined with H_1-antihistamine failed to produce a substantial advantage for urticaria symptoms compared to antihistamine administered in monotherapy [33, 43].

A recent study has shown that both ASA and food additives determine a significant increase in urinary LTE_4 levels after oral specific challenge only in patients with hypersensitivity to ASA or HFA [44]. When urinary LTE_4 levels were compared between patients with CU and hypersensitivity to ASA or HFA, patients with CU but tolerating both ASA and food additives, and healthy subjects, no difference was found at baseline between the three groups, whereas an increase in urinary LTE_4 levels was found after aspirin and food additives only in the former groups. With regard to urinary LTE_4 levels, no differences have been found in patients with hypersensitivity to ASA or patients with HFA after the specific challenge. These results might also explain the good response to therapy with leukotriene receptor antagonists reported in most unselected patients with CU [44], and the failure of these in selected patients with very chronic idiopathic urticaria [33].

In conclusion, only 16 of our 838 patients with a clinical history related to food and both positive $DBPC_{mixed}$ and $DBPC_{single}$ challenges presented an improvement in urticaria during the FAFD period. However, the combination of the results of FAFD and of challenge tests with a mixture of additives seems to be of considerable practical interest for allergists, internists and dermatologists, rather than clinical history data and the results of $DBPC_{single}$ challenges, in patients with RCIU. The results may be helpful in cases of refractory CU/angioedema that do not respond completely to H_1-antihistamine therapy.

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