

Short communication

Role of nonallergic hypersensitivity reactions in children with chronic urticaria

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Background IgE-independent (pseudoallergic) reactions to food and food ingredients are common in a subgroup of adult patients with chronic urticaria, who have daily spontaneous occurrence of wheals. However, for children with chronic urticaria (duration longer than 6 weeks, no physical influence), no data on the importance of pseudoallergen-induced chronic urticaria are available. Therefore, we investigated the role of nonallergic hypersensitivity to food in all children seen with chronic continuous urticaria in our two clinics over the last 2 years ($n=16$).

Methods All patients were given a low-pseudoallergen diet for 3 weeks followed by provocation with food rich in pseudoallergens. To identify the main eliciting agents, a subgroup of responders was exposed to food additives by double-blind, placebo-controlled food challenges.

Results Pseudoallergen-induced urticaria was diagnosed in 12 cases (75%). Reactions occurred mainly to coloring agents and preservatives, but also to monosodium glutamate and a sweetener (saccharin/cyclamate).

Conclusions These results confirm that nonallergic hypersensitivity reactions play a role in children with chronic urticaria, although the latter disease is rare at that age. In children, food additives, especially coloring agents and preservatives, appear to play a more important role in eliciting nonallergic hypersensitivity reactions than in adult patients, where naturally occurring pseudoallergens in fruits and vegetables are mainly responsible.

Key words: children; chronic urticaria; diet; food intolerance; nonallergic hypersensitivity; pseudoallergy.

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Food- and drug-related reactions mimicking allergic reactions without specific sensitization of the immune system are well known. Several terms have been used to describe these reactions, such as "idiosyncrasy", "intolerance", "pseudoallergy", and "nonallergic hypersensitivity", among others. In chronic continuous urticaria, which is characterized by a duration of more than 6 weeks, daily spontaneous occurrence of wheals, and exclusion of acute, intermittent, and physical forms of urticaria, nonallergic hypersensitivity reactions to food and food additives have been reported repeatedly (1, 2). In a prospective study in adult patients hospitalized for chronic urticaria, it could be confirmed that 73% of the patients with daily spontaneous occurrence of wheals benefited from a strict elimination diet avoiding all food additives as well as natural foods known to cause urticaria, such as tomatoes, berries, matured cheese, and alcohol (3).

However, in children, no data on the importance of pseudoallergen-induced chronic urticaria are available, possibly because chronic continuous urticaria is rarely seen at that age. In the literature, only a few studies have investigated the pathogenesis of urticaria in children (4–11). However, because the terminology for the different forms of urticaria has been used inconsistently and the term "chronic urticaria" – in contrast to the stringent criteria mentioned above – has been used to denote also physical forms of urticaria, the interpretation of the results of these studies regarding the importance of food- or food additive-induced urticaria is difficult. In these studies, physical forms of urticaria (mainly urticaria factitia) accounted for most of the identified eliciting factors (4, 6, 10). Apart from one study (9), food and food additives played only a minor role (4, 5, 10). Unfortunately, the methods of diagnosis are often

poorly documented. In one study, food additives and acetylsalicylic acid are listed together as a causative factor (6); thus, the relevance of food additives on their own is not known.

Therefore, we conducted a prospective study at the departments of Pediatrics and Dermatology of the Charité, Berlin, to assess the role of food allergy and nonallergic hypersensitivity in chronic urticaria in children.

Material and methods

Patients

All children with moderate to severe chronic continuous urticaria of at least 3 months' duration, seen from 1995 to 1997 ($n=16$, mean age 12 years, range 3–17 years), were included in the study. The severity was documented by a score ranging from 0 to 3, as used in a previous study in adult patients with chronic urticaria (3). Nine children were seen on an outpatient basis, and seven patients were hospitalized.

Diet

All patients were put on a special strict elimination diet until remission of symptoms (Table 1). In view of the fact that in adult patients remission of symptoms usually occurs within 2 weeks, the diet was followed for 3 weeks.

Laboratory tests

IgE-mediated allergy as a cause of whealing was excluded by patient history and skin prick test or investigation of specific IgE in serum (Pharmacia CAP System).

Food challenge

Oral provocation tests were performed by reintroduction of normal food in all patients having improved on elimination diet in order to establish the diagnosis of pseudoallergy/nonallergic hypersensitivity, and by double-blind, placebo-controlled exposure to food additives – those known to elicit nonallergic hypersensitivity – in gelatin capsules (Table 2) in a subgroup of patients. Since non-allergic hypersensitivity reactions, in contrast to IgE-mediated allergic reactions, often occur with a latency of only 6–24 h, only one challenge test was performed per day. After positive reactions, testing was stopped until symptoms ceased. Symptomatic treatment (preferably antihistamines) was given only in the case of intolerably severe reactions.

Results

Of 16 patients, 13 (81%) (six hospitalized, seven on an outpatient basis) went into remission under a stringently controlled low-pseudoallergen diet. Nine of them were free of symptoms within 10 days of diet. Three patients improved considerably but continued to show a few wheals for several weeks. Finally, symptoms ceased completely. All of these children continued to react with wheals after accidental mistakes or discontinuation of the diet. However, on adherence to the diet, none of them needed any medication. These cases were diagnosed as pseudoallergen-induced urticaria. One 17-year-old patient improved on diet but did not respond to reintroduction of prohibited food. Her symptoms ceased completely after eradication of *Helicobacter pylori*.

One hospitalized patient and two outpatients failed to respond to the diet. In order to identify

Table 1. Low-pseudoallergen diet. Strictly forbidden: all food containing preservatives, dyes, or antioxidants; all industrially processed food should be carefully checked for additives (Zuberbier et al. [3])

Allowed		Forbidden
Basic food	Preservative-free bread, potatoes, rice, unprocessed cereals, flour (not self-raising!), rice cakes, durum wheat pasta (without egg)	All others (e.g., pasta with eggs, cake, biscuits, potato chips)
Fats	Butter, cold-pressed plant oils	All others (e.g., margarine, mayonnaise)
Milk products	Fresh milk, cream without stabilizers, white cheese, fromage frais, small amount of mild Gouda cheese	All others
Food from animals	Fresh meat without seasoning	All others including eggs, seafood, smoked meat
Vegetables	All except those listed as forbidden (e.g., lettuce, carrots, zucchini, cabbage, broccoli, asparagus)	Artichokes, peas, mushrooms, spinach, rhubarb, tomatoes and tomato products, olives, sweet peppers, spinach
Fruit	None	All, including dried fruits or fruit juices
Herbs, spices, seasoning	Salt, sugar, chives, onions	All others including garlic and other herbs
Sweets	None	All, including chewing gum
Beverages	Milk, mineral water, coffee, black tea	All others including beer, wine, spirits, and herbal teas
Spreads	Honey	All others

Table 2. Pseudoallergens used for provocation tests (masked in gelatin capsules)

Pseudoallergens	Name	E number	Dose (mg)
Coloring agents			
Azo dyes	Tartrazine	E102	50
	Sunset yellow	E110	5
	Azorubine	E122	5
	Amaranth	E123	5
	Ponceau	E124	5
	Brilliant black BN	E151	5
Other synthetic dyes	Quinoline yellow	E104	5
	Erythrosine	E127	5
	Patent blue	E131	5
	Indigotine	E132	5
Natural colors	Iron(III) oxide, red	E172	5
	Cochineal	E120	5
Preservatives			
	Sorbic acid	E200	1000
	Sodium benzoate	E211	1000
	p-Hydroxybenzoate	E214-219	1000
	Sodium metabisulfite	E223	50
	Sodium nitrate	E251	100
Antioxidants			
	Butylhydroxyanisol (BHA)	E320	50
	Butylhydroxytoluol (BHT)	E321	50
	Propylgallate	E310	50
	Tocopherol	E306-309	50
Taste enhancers	Monosodium glutamate	E621	200
Naturally occurring substances	Salicylic acid		100

the main eliciting agents in children with pseudoallergen-induced chronic urticaria, double-blind, placebo-controlled food challenges (DBPCFC) with food additives were performed in six children. Only one patient with proven pseudoallergy did not react after DBPCFC. The outcome of the food challenges is documented in Table 3. The main eliciting agents were preservatives and coloring agents. In one child, a sweetener (saccharin/cyclamate) was also tested because of an implication in the patient's history, and it proved to cause positive reactions. This child was rechallenged by DBPCFC 1 year later. Reactions to the sweetener were still positive, while other food additives which caused wheals 1 year before were negative.

Discussion

In our study, 12 of 16 patients with chronic continuous urticaria (75%) were diagnosed as suffering from nonallergic hypersensitivity, a result which is in line with the results in adult patients (73%) (3). The time needed before the patients went into remission clearly points to a nonallergic mechanism of reaction. In IgE-mediated allergy, whealing generally ceases shortly after elimination of the

allergen. In one case, there was an improvement in diet, but remission of all symptoms occurred only after eradication of *H. pylori*. Since food challenge in this patient was negative (in contrast to the other patients' improvement on diet), a direct effect of the food can be excluded. However, until now, it was unclear whether *H. pylori* itself or the inflammation caused by the infection was responsible. Therefore, in this patient, the diet might have influenced symptom severity by an indirect effect on gastric inflammation through the elimination of fatty, sour, and spicy food.

DBPCFC in six patients revealed that food additives caused 83% of nonallergic hypersensitivity reactions. The reactions were mainly to coloring agents and preservatives but also to monosodium glutamate and a sweetener (saccharin/cyclamate). Coloring agents, especially tartrazine, and preservatives such as benzoic acid have previously been implicated in provoking urticarial reactions in children (6, 8-12). Only a few other studies have documented reactions to glutamate in children (7, 8, 13). In adults, nonallergic hypersensitivity reactions to glutamate are well documented, although urticaria is rarely mentioned (14, 15). Studies investigating the potency of sweeteners to induce nonallergic hypersensitivity reactions are rare. One study asserts that saccharin can provoke urticaria (16), and another study found that aspartame causes whealing (17). However, Garriga et al. (18) found that hypersensitivity reactions to aspartame

Table 3. Positive reactions to individual pseudoallergens after double-blind, placebo-controlled food challenge in six patients. In 5/6 patients, eliciting food additives could be identified. One child was negative

Patient no.	Eliciting agents
1	Azo dyes (see Table 2) Iron(III) oxide red Sorbic acid p-Hydroxybenzoate
2	Erythrosine Patent blue V Indigotine Quinoline yellow Iron(III) oxide red
3	Sorbic acid p-Hydroxybenzoate Monosodium glutamate Saccharin/sodium cyclamate
4	Mixture of coloring agents (quinoline yellow, sunset yellow, azorubine, patent blue) Sorbic acid Benzoic acid
5	p-Hydroxybenzoate

were not reproducible. A recent study demonstrated that the sweetener aspartame was no more likely than placebo to cause urticaria (19).

One child did not respond to oral provocation with encapsulated food additives, but did react repeatedly after food rich in pseudoallergens. This phenomenon is rarely seen in children but is often observed in adult patients. While 73% of patients with chronic urticaria improved markedly on a low-pseudoallergen diet and reacted to reintroduction of normal (pseudoallergen-containing) food, only 19% of DBPCFC with encapsulated food additives were positive (3). The observation that one child with pseudoallergy did not react to challenges with encapsulated food additives confirms that naturally occurring pseudoallergens can cause wheals also in children, although to a lesser degree than in adults. Thus, only a diet which avoids both groups of pseudoallergens, namely, food additives and naturally occurring pseudoallergens, will identify all cases of nonallergic hypersensitivity in childhood. Therefore, the often-used additive-free diet should be replaced by a strict low-pseudoallergen diet.

Most studies describe chronic urticaria in children as a self-limited disease (5, 6, 8). In a follow-up study, Pollock & Warner (7) found that at least 26 out of 34 children (76%) did not react to rechallenge; in only two children could urticaria still be provoked. However, they did not react to the whole range of food additives initially found to be positive. This finding is in line with the observation that one of our patients reacted only to saccharin/cyclamate on rechallenge after 1 year, but not to preservatives and monosodium glutamate.

From a nutritional point of view, the low-pseudoallergen diet provides a good basis for a balanced diet without the risk of deficiencies. However, since food aversions in childhood are common and forbidden foods therefore cannot be replaced easily, the diet may not always be as balanced as it should be. To avoid deficiencies and maintain compliance, it is very important to enlarge the list of foods allowed as soon as the diagnosis of pseudoallergy/nonallergic hypersensitivity is confirmed. Formerly prohibited foods should be reintroduced step by step. The order of introduction should be determined with regard to the unlikelihood of certain foods to cause reactions and to the preferences of the patient (for further information, see Ehlers & Zuberbier [20]). The procedure of enlarging the list of food allowed can be performed on an outpatient basis.

In conclusion, our findings confirm that non-allergic hypersensitivity reactions play a role in children with chronic urticaria, although the latter disease is rare in childhood. The management of

food-induced chronic urticaria by diet requires highly motivated families. However, our data indicate that this method is worth trying.

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