

Pseudoallergen-free Diet in the Treatment of Chronic Urticaria

A Prospective Study

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In chronic urticaria, the possible pathogenetic role of pseudoallergic reactions to food has been repeatedly discussed, but stringent prospective studies regarding their clinical significance are not available.

All patients with chronic urticaria and/or angioedema hospitalized at the department of dermatology during a period of 2 years were therefore included in a prospective study. Patients ($n = 64$) were screened for common causes of urticaria and then evaluated for possible benefits of a stringently controlled pseudoallergen-free diet. Double-blind, placebo-controlled oral provocation tests with food additives were performed on those patients benefitting from diet.

In 73% of patients, symptoms ceased or were greatly reduced within 2 weeks on diet, although only 19% of them responded to individual pseudoallergens on provocation tests. Of the remaining patients, 11% responded to treatment of an associated inflammatory disease, and in 16%, no cause of the urticaria was ascertained. Follow-up at 6 months after hospitalization showed complete remission on diet in 46% and lasting improvement in all but one of the remaining patients on diet.

An additive-free, stringently controlled diet thus provides a simple means of diagnosing and treating the majority of patients with chronic urticaria. *Key words: angioedema; food intolerance; pseudoallergy; additive-free diet.*

(Accepted May 24, 1995.)

Acta Derm Venereol (Stockh) 1995; 75: 484-487.

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Chronic urticaria is defined as wealing and/or angioedema lasting longer than 6 weeks and occurring at least twice a week. The condition is often regarded as idiopathic, since according to the literature eliciting factors can be identified in only 10-20% of these patients (1, 2). Infections, drug reactions, pseudoallergic reactions to food additives, type I allergy or autoantibodies have been suggested as possible causes, although the clinical relevance of these findings has remained controversial (3-7).

Pseudoallergic reactions to food additives are particularly difficult to diagnose. In contrast to genuine allergic reactions, which are clinically mimicked by pseudoallergic reactions, sensitization of the immune system is not involved, and skin tests or in vitro tests thus cannot be employed for diagnostic purposes. In the past, encouraging therapeutic results have nevertheless been repeatedly reported in patients on an additive-free diet (4, 8, 9). These studies have, however, been criticised for not being well controlled, for lacking an exact monitoring of disease severity and for their loose definition of a positive response (10, 11).

The current prospective study was therefore initiated to systematically examine the role of pseudoallergic reactions to food in chronic urticaria under stringent conditions.

PATIENTS AND METHODS

Patients

All patients with chronic urticaria ($n = 67$, mean age 42 years, range 16 to 63 years, 21% male, 79% female) admitted from May 1992 until May 1994 underwent a standardized diagnostic and therapeutic regimen. Hospitalization did not reflect a special selection of patients but took place routinely for the purpose of an extensive diagnostic work-up. The patients had a 3-month history of urticaria and/or angioedema (66% urticaria only, 25% urticaria and angioedema, 9% angioedema only) with moderate to severe daily symptoms (score of 2 or 3, as defined below) that were not controlled satisfactorily by antihistamines. All patients had stopped antihistamines 2 days (in case of astemizole 2 months) and corticosteroids 2 weeks prior to admission. Informed consent was obtained in each case for participation in the study at the time of admission.

Patient evaluation

The attending physician kept a daily record of visible symptoms on which evaluation was based. For quantification of reactions, the following score was used: 0 = no symptoms, 1 = mild (< 10 weals or an angioedema, diameter < 2 cm), 2 = moderate (disseminated, non-confluent weals of limited extension; up to 3 lesions of angioedema, each < 10 cm in diameter), 3 = intense (large areas of confluent weals; diameter of angioedema > 10 cm). Independently of the physician's recordings, patients were asked to keep a daily diary of symptoms. This was used to train patients to keep an exact diary, so as to ensure a standardized follow-up and an optimal compliance. Patients were instructed to show all newly developing lesions to a doctor, also at night to the physician on call. Evaluation of treatment success was based on the score comparing levels at the time of admission and while on diet. Remission was defined as a reduction of daily symptoms to < 10 weals (score 1) or no weals (score 0).

Diet

All patients were given a standardized diet. For the first 3 days, only freshly cooked, unsulphited potatoes, polished rice, water and salt were allowed. A less restrictive diet was then instituted, which was free of artificial additives and of known naturally occurring pseudoallergens like salicylates (see Table I). This diet had been especially designed, based on previous experience during a pilot phase of the study. Furthermore, a placebo effect had been ruled out in another pilot study with 3 patients, where a comparison with a diabetes diet was made in a double-blind cross-over design, with 3 weeks on each diet. In all 3 patients, improvement of the urticaria was only seen on the pseudoallergen-free diet (unpublished).

Laboratory tests

On admission, blood tests were taken for total blood count and differential, ESR, electrolytes, glucose, liver enzymes, creatinine, urea, serum protein electrophoresis, immunoglobulins, TPHA, ANF, C3, C4, T3, T4, TSH, thyroid antibodies, total IgE and *Candida* RAST. Three consecutive stool specimens were tested for *Candida*, eggs and parasites. In cases presenting with angioedema alone, C1-esterase inhibitor levels and function were checked as well.

Skin tests

Prick testing with common allergens was performed for screening of type I allergies in all patients. In patients suspected to suffer from

Table I. Pseudoallergen-free diet

Strictly forbidden:

all food containing preservatives, dyes or antioxidants (all kinds of industrially processed food should be regarded with suspicion).

	Allowed	Forbidden
Basic food	Preservative-free bread, potatoes, rice, unprocessed cereals, flour	All others (e.g. noodles, potato chips)
Fat	Butter, cold pressed plant oils	All others (e.g. margarine)
Milk products	Fresh milk, cream, white cheese, young Gouda	All others
Meat, fish, eggs	Fresh meat	All others, incl. seafood
Vegetables	All, except those listed as forbidden	Artichokes, peas, mushrooms, rhubarb, tomatoes, olives, sweet pepper
Fruits	None	All
Herbs, spices	Salt, sugar, chives	All others
Sweets	None except honey	All (chewing gum)
Beverages	Milk, water, coffee, black tea	All others

allergy to specific foods, native food samples were used for prick testing as well. Skin tests for cold, heat and pressure urticaria were conducted as described before (13).

Oral provocation tests

Known pseudoallergens (see Table II) were exposed under double-blind, placebo-controlled conditions in gelatine capsules. The capsules were given together with breakfast in order to mimic the intake of additive-rich food. Oral provocation tests were performed on all patients improving on diet. Only one group of additives was exposed per day, since pseudoallergic reactions, unlike IgE-mediated reactions, usually occur with a latency of up to 24 h. Positive reactions were confirmed by repeated testing on a later day. Placebo capsules were given on at least 3 different days throughout the test period. After strong reactions, no provocation tests were performed for the subsequent 2

Table II. Pseudoallergens used for provocation tests (masked in white gelatine capsules, labelled A-J)

- A) food dyes: quinoline yellow (E 104, D&C yellow no.10), sunset yellow (E110, FD&C yellow no.6), cochineal (E120) azorubine (E122), amarante (E123), ponceau 4R (E124), erythrosine (E127, FD&C red no.3), patent blue V (E131), indigotine (E132, FD&C blue no.2), brilliant black BN (E151), iron(III)oxide red (E172), 5 mg each
- B) sorbic acid, 1,000 mg
- C) sodiumbenzoate, 1,000 mg; p-hydroxybenzoate, 1,000 mg
- D) sodiummetabisulfite, 100 mg
- E) placebo: lactose
- F) sodiumnitrate, 100 mg; sodiumglutamate, 200 mg
- G) tartrazine, 50 mg
- H) salicylic acid, 100 mg
- J) butylhydroxyanisol, butylhydroxytoluol, propylgallate, tocopherol, 50 mg each

Dosages are based on quantities of the individual agents found in additive-rich German food consumed in one day. The amount of dyes used in food can be higher in other countries.

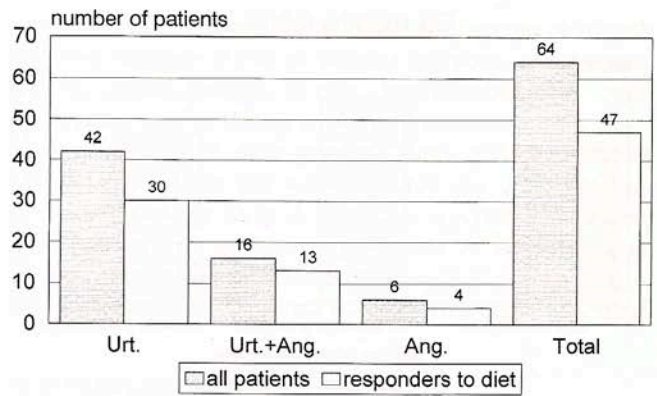


Fig. 1. Number of patients presenting with urticaria and/or angioedema and number of patients responding to a pseudoallergen-free diet.

days in order to avoid testing in a period of pharmacological tachyphylaxis. Symptomatic treatment (preferably antihistamines) was only given in case of intolerably severe reactions.

Other diagnostic procedures

ECG and a chest X-ray were part of the routine diagnostic procedures. Additional investigations, e.g. gastroscopy, were only conducted in patients with specific symptoms.

Follow-up

Patients were followed-up for 6 months after discharge from hospital (at time of writing 56 of 64 patients). Follow-up could be completed in 49 of these 56 patients. Seven patients were lost, having moved.

RESULTS

Of the 67 patients included in the study, 3 dropped out during the first 2 weeks because of lack of compliance with the diet ($n=1$) or because they needed drug treatment for concomitant diseases (one each for bronchial asthma and rheumatoid arthritis).

Of the remaining 64 patients, 47 (73.4%) went into remission within 2 weeks on diet. No differences were observed in patients suffering from urticaria, angioedema or both (Fig. 1). An improvement of the urticaria score was observed mostly during the first 5 days, although in about one third of patients, remission was seen only after more than 1 week on diet.

In 19% of patients ($n=9$) who had improved on diet, individual additives (see Table III) caused reproducible, objective symptoms on provocation tests.

Table III. Positive reactions to individual pseudoallergens after oral provocation

Number of patients reacting	Agent
3	Salicylates
5	Dyes
3	Sulfites
1	Sorbic acid

In 9 of 47 patients reacting to additive-rich food by history, reactions to specific eliciting pseudoallergens (in three cases two factors) were noted on oral provocation.

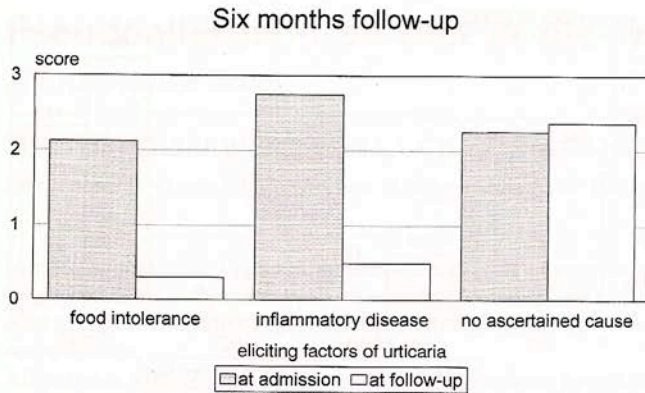


Fig. 2. Mean score of urticaria at admission and at follow-up after 6 months in patients with either pseudoallergic food intolerance ($n=39$), with urticaria related to inflammatory or infectious diseases ($n=4$), or in those patients where no cause could be ascertained ($n=6$).

In patients responding to diet, thyroid autoantibodies were detected in 6% ($n=3$) and an intestinal candidiasis in 21% ($n=10$). None had, however, a positive RAST for *Candida*-specific IgE. Parasites were detected in 3 cases (lambliaosis in 2 cases and oxyuriasis in one case, respectively). Candidiasis and parasitosis were only treated after evaluation of diet success, and specific drug treatment of these conditions did not cause additional improvement of the urticaria. No type I allergic reactions to food allergens were detected.

In 7 patients (10.9%), urticaria failed to improve on diet but could be clearly related to infectious or inflammatory processes. In these patients, symptoms ceased or improved after treatment of a *Campylobacter pyloris*-positive gastritis ($n=4$), a reflux gastritis ($n=2$) or a posthepatic cholestasis because of benign papillary stenosis ($n=1$), respectively.

In 10 patients (15.6%), no unequivocal specific eliciting factor of the urticaria could be determined. Among them, 3 had thyroid abnormalities, with 2 suffering from Grave's disease and one having high levels of antimicrosomal thyroid antibodies (1000 U/ml).

In all patients, the prevalence of atopic diseases was only 10% (defined as positive prick tests for one or more allergens in combination with atopic symptoms); thyroid autoantibodies were noted in 9% ($n=5$), decreased complement factors C3 and C4 in 14%, and low positive ANF in one patient (no pathological relevance, with a titer of 1:320). None of the other blood tests yielded pathological findings.

Stool cultures were pathological (more than 20 colonies per plate) for *Candida* in 19% ($n=12$).

Tests for associated cold or heat urticaria were negative in all cases. Urticaria factitia was seen in 25 cases, cholinergic urticaria in 4 cases and pressure urticaria in four cases (in some cases in combination).

Follow-up

At follow-up after 6 months ($n=49$), partial or complete absence of symptoms had been maintained in 38 of 39 patients benefitting from diet. The mean score of patients with lasting improvement after 6 months was 0.22, compared to 2.12 prior to admission (Fig. 2). Only 6 patients were still in need of anti-

histamines on rare occasions, whereas before hospitalization, all of them had needed a daily medication with antihistamines or corticosteroids. In 18 of the 39 patients benefitting from diet, urticaria had totally cleared; they tolerated again a normal diet and their urticaria could no longer be provoked by additive-rich food.

One patient who still suffered from intense urticaria had totally discontinued the diet, although he had improved while in hospital.

Most patients in remission admitted that they had not always adhered strictly to the diet and had sometimes purposely broken it, e.g. when they had been invited to important social events. They reported that this was inevitably followed by transiently intensified whealing. All patients had tried to eat some food items originally not allowed in the diet, such as a special type of fruit, without worsening of their symptomatology, and could thus diversify their diet. Tolerance to these forbidden items was often noted to be dose-dependent or limited to a special subgroup of fruits or vegetables. Thus, some patients reacted only to ripe farmland tomatoes, whereas young greenhouse tomatoes could be eaten without problems.

Of those patients where no cause of the urticaria could be ascertained, 6 have been followed up so far. Five of them still suffered from urticaria of the same intensity as before (mean score prior to admission 2.25, versus 2.16 at 6 months' follow-up). In 2 patients, a spontaneous remission had occurred.

In the group of urticaria patients with associated infectious or inflammatory diseases, 4 patients have been followed up. Three have remained completely free of symptoms, whereas in one patient with *Campylobacter*-positive gastritis, the urticaria had ceased with treatment of *Campylobacter* but had recurred at a low level (score 1) after some months, together with new clinical signs of gastritis.

DISCUSSION

In the present study, the majority of patients with chronic urticaria were found to suffer from pseudoallergic or intolerance reactions, terms that are used for non-immunologically mediated processes which clinically resemble allergic reactions. Although the first report of an intolerance reaction due to aspirin was published in 1902 (14), the pathomechanisms involved have remained unclear. A clinically important feature is the slow onset of symptoms (up to 24 h after contact, with 50% of reactions occurring within the first 6 h) (4), in contrast to the rapidly occurring IgE-mediated reactions. Whealing can last for several days after provocation of pseudoallergic reactions, despite the absence of further contact with the eliciting agent.

Pseudoallergic reactions to foods or food additives have frequently been discussed as a cause of chronic urticaria (4, 8, 9, 11). Compared to the vast number of additives used in food processing – estimations range between 2,000 and 20,000 (11) – a surprisingly small number are known to cause adverse reactions. However, not only artificial additives must be incriminated; naturally occurring substances, especially salicylates which are found at high concentrations in several types of fruits, vegetables and spices (15), must also be considered. Quantities of these naturally occurring pseudoallergens can vary consid-

crably in the same type of fruit or vegetable depending on type, age and place of origin. Because of the dose dependency of pseudoallergic reactions, this might lead to misinterpretation of reactions.

In the present study, we chose a very strict diet for diagnostic as well as therapeutic purposes in patients with chronic urticaria. The diet was designed to avoid possible concealed pseudoallergens like colorants in eggs or in farmed salmon, the latter being fed canthaxanthin to imitate the colour of wild salmon (10).

The high responsiveness to diet observed in the present study can be explained in part by the good patient compliance to the rather rigid dietary regimen and in part by the well-monitored evaluation procedure. A placebo effect must be considered in every therapy but appears to be of little relevance here, since the follow-up showed that involuntary mistakes in the diet were followed by urticaria. The diet had also been shown to be effective in a preliminary double-blind cross-over design compared to a pseudoallergen-rich diabetes diet. Furthermore, improvement on pseudoallergen-free diet occurred in more than one third of the patients only after 5–14 days on diet, which can be explained by the protracted nature of pseudoallergic reactions. This fact must be kept in mind by patients and physicians, as responders to pseudoallergen-free diet can otherwise easily be missed.

Follow-up of patients after hospital discharge showed a lasting response to diet which could be individually modified and diversified. No difference was seen in the response of patients with urticaria and/or angioedema, which is particularly encouraging since angioedema is generally considered to be more difficult to handle than wealing alone.

Intestinal candidiasis is frequently mentioned as the cause of chronic urticaria in older literature (3), but judging from the present study, its pathological significance appears low since wealing ceased under diet alone. An increased prevalence of thyroid autoantibodies has also been reported in chronic urticaria (16). The pathophysiological relevance of these antibodies has, however, been questioned by the same authors, in agreement with our observations that these patients improved on diet alone. The causative role of autoantibodies in chronic urticaria is nevertheless in need of further clarification, also in view of the recently reported high-affinity IgE receptor autoantibodies in some patients with chronic urticaria by Hide et al. (6).

In the present study, the beneficial effect of a strictly observed pseudoallergen-free diet stands in contrast to the low rate (19%) of positive reactions during provocation tests with individual known pseudoallergens. Possible explanations for this discrepancy might be: 1) the dose-dependency of pseudoallergic reactions; 2) the requirement for a combined or synergistic effect of several additives; 3) the need for interaction of pseudoallergens with other food ingredients; or 4) the existence of hitherto unknown pseudoallergens which were not used for testing.

The 19% response rate on provocation tests is lower than that reported in studies of the 1970's, reviewed by Juhlin (17). These studies were, however, open or single-blind and not stringently controlled. Kellet et al. (18) who employed double-blind, pla-

cebo-controlled tests in gelatine capsules, observed in contrast only low numbers (12%) of positive reactions, in agreement with the present findings. It seems thus sensible to no longer perform this form of testing as part of routine diagnostic procedures in urticaria. A more practical, time-, and cost-reducing alternative would be the well-monitored use of a pseudoallergen-free diet for about 3 weeks, as reported here. Future investigations will have to be performed on outpatient populations in order to evaluate the importance of pseudoallergies in a less stringently controlled but more cost-effective setting.

ACKNOWLEDGEMENT

This study was supported by a grant PUG (Program Environment and Health) from the German Kernforschungszentrum Karlsruhe based on funds of the Land Baden-Württemberg (91/010/PAUL).

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