SHORT REPORT

Histamine intolerance in patients with chronic spontaneous urticaria

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Abstract

Background Histamine intolerance and pseudoallergy to foods have been suggested to be causes of chronic spontaneous urticaria (CSU) with some patients reporting exacerbation with histamine-rich foods.

Objective The study aim was to identify the rate of histamine-intolerant CSU patients and to characterize the relevance of histamine intolerance as an underlying cause of CSU.

Methods A cohort of 157 of moderate to severe CSU patients (UAS7 $\geq$ 10) was asked to provide a detailed clinical history, particularly in relation to symptom development after eating histamine-rich foods. They subsequently undertook a histamine-free pseudoallergen-low diet followed by a double-blind, placebo-controlled oral histamine provocation (75 mg).

Results One third of patients (34%) had a positive history of histamine intolerance. There was no statistical difference between the mean UAS7 scores of patients with positive and negative histories (22.4 $\pm$ 1.0 vs. 22.7 $\pm$ 0.8). When kept on diet, 46% of patients responded with reduced CSU activity (UAS7 reduction of $\geq$7). Following double-blind, placebo-controlled oral histamine provocation, 17% of patients gave a positive weal response. There appeared to be little relationship between patient history, response to diet and the weal response to oral histamine provocation. First, the history-positive and -negative groups contained similar proportions of diet and histamine provocation weal-positive patients. Second, the diet-positive and -negative groups contained similar proportions of history-positive and histamine provocation weal-positive patients. Third, the histamine provocation weal-positive and -negative groups had similar rates of history- and diet-positive patients. Finally, only 2 of the 157 patients were positive in all three domains.

Conclusions CSU due to histamine intolerance appears to be rare and cannot be diagnosed based on the history. The study confirms that avoidance diets low in pseudoallergens can improve urticaria symptoms, this is probably not due to the absence of dietary histamine.

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Conflicts of interest

All authors declare no conflict of interest.

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Introduction

Chronic spontaneous urticaria (CSU) is a frequent skin disease characterized by recurrent weals and/or angioedema for more than 6 weeks.[1] In CSU, chronic infections, autoreactivity and intolerance to food components have been suggested as causes.[1,2] Food intolerance is different from IgE-mediated food allergy because it involves pseudoallergic reactions to artificial additives such as colourants, antioxidants, flavourings, natural aromatic compounds and histamine.[2]

Histamine intolerance is defined by the occurrence of pathological signs and symptoms in response to histamine in food. It is thought to result from a disequilibrium between accumulated histamine and the capacity for histamine degradation.[3] The signs and symptoms of histamine intolerance include diarrhoea, headache, rhinoconjunctivitis, asthma, hypotension, pruritus and flushing as well as weals and angioedema, all of which typically occur after the intake of foods that are rich in histamine, such as wine and mature cheese. Histamine is a major mediator in the induction of weals and angioedema in CSU. Histamine intolerance has been claimed to cause CSU with some patients reportedly experiencing exacerbations of symptoms upon ingestion of histamine-rich foods.[4–7] Also, CSU activity can be reduced by a

histamine-free diet and H_1-antihistamines.[1,2,8–17] However, most histamine-free diets are also low in other pseudoallergens.

The diagnostic work-up of histamine intolerance includes a thorough patient history, the elimination of dietary histamine-rich foods and double-blind, placebo-controlled oral histamine provocation, although it is recognized that this last procedure may provoke a positive response in some healthy individuals.[18] The prevalence and relevance of histamine intolerance in CSU remain unclear. Our study aim was to identify the rate of histamine-intolerant CSU patients and to characterize the relevance of histamine intolerance as an underlying cause of CSU. Consequently, CSU patients were asked to provide a detailed clinical history, particularly in relation to symptom development after eating histamine-rich foods. They subsequently undertook a histamine-free diet followed by a double-blind, placebo-controlled oral histamine provocation.

Methods

This is a retrospective analysis of consecutive 157 patients at the specialist urticaria clinic, Department of Dermatology and Allergy, Charité-Universitätsmedizin, Berlin, Germany, who were diagnosed with moderate to severe CSU (UAS7 $\geq$ 10).[1] These patients comprised 118 females and 39 males, median age 43 years (range 17–79 years) with a median duration of their disease of 2 years (range 4 months to 50 years).

History of histamine intolerance

As part of obtaining their clinical history, patients were shown a list of histamine-rich foods and biogenic amines and asked whether they had ever experienced weals in response to eating any of them.[13,19]

Histamine-free diet

Patients were then asked to follow a specific diet for 31 days. During this period, patients recorded their urticaria activity scores (UAS)[1] on each day of the dietary study. From day 1 to day 7, patients maintained their normal dietary habits. On days 8–10, patients ate or drank only rice, potatoes, bread and butter, oil, salt, coffee and tea. On days 11–31, patients followed a histamine-free and pseudoallergen-low diet.[1,2,20] The responsiveness of patients to this diet was calculated from the difference between the UAS7 scores for days 1–7 and days 25–31. Patients were requested not to take H_1-antihistamines during these periods. The categories of response and their criteria were: positive response, UAS7 improvement $\geq$7; negative response: UAS7 improvement <7.

Double-blind, placebo-controlled oral histamine provocation

On day 32, patients were admitted to undergo a 2-day in-patient double-blind, placebo-controlled oral histamine provocation while still following the histamine-free pseudoallergen-low diet. Verum [75 mg histamine (equivalent to 125 mg histamine dihydrochloride) plus 125 mg of sucrose] and placebo (125 mg of sucrose) were placed in identical gelatine capsules, which were swallowed by the patient. Verum and placebo were administered in a randomized fashion at the same time on alternate days, 6 h after the last meal and 6 h before the next meal. Patients avoided alcohol, non-steroidal anti-inflammatory drugs and strenuous exercise on challenge days. Immunomodulating medications and H_1-antihistamines were discontinued at least 7 days beforehand. Both physicians and patients recorded the appearance of symptoms, e.g. weals, itching, redness, angioedema and diarrhoea, which occurred within 24 h of each challenge.

Statistics

UAS7 scores are presented as means $\pm$ SEMs and the significance of differences was calculated by Student's *t* test for paired data. The significance of differences between the numbers of patients in particular groups was calculated using Fisher's exact test.

Results

Fifty-three (34%) patients had a positive history of histamine intolerance. There was no statistical difference between the mean UAS7 scores of patients with positive and negative histories (22.4 $\pm$ 1.0 vs. 22.7 $\pm$ 0.8).

When patients were kept on a histamine-free and pseudoallergen-low diet, 72 (46%) responded (reduction of $\geq$7 UAS7 points, Table 1). The mean reduction in UAS7 of the diet-positive patients was 59% ($P < 0.0001$). Using similar criteria to Magerl *et al.* [2] for defining responder groups to diet, 23 patients responded strongly and 49 had a partial response, with improvements in UAS7 of 73% and 45% respectively (both *P*s < 0.001). Of the remaining patients, 76 (48%) had no response to diet and 9 (6%) were worse. There was no statistical difference ($P = 0.143$) between the mean pre-diet UAS7 scores of diet-positive patients (23.6 $\pm$ 1.0) and patients who did not improve (21.8 $\pm$ 0.8).

Of the 157 patients who received double-blind, placebo-controlled oral histamine provocation, 60 (38%) had a positive response in that they developed weals, itching, redness and/or diarrhoea to histamine, but no reaction to placebo (Table 1). In addition, three patients reacted to placebo only, three reacted to both, and 91 were provocation negative to both placebo and histamine. Urticarial reactions, i.e. weals in response to oral histamine but not placebo provocation, occurred in 27 (17%) CSU patients. There was no statistical difference between the initial mean UAS7 scores of histamine weal-positive patients (24.4 $\pm$ 1.3) and histamine weal-negative patients (22.2 $\pm$ 0.7).

The most important finding from our analyses is the relationship between the three major outcomes, patient history, response to diet and the weal response to oral histamine provocation (Fig. 1). First, of the 53 history-positive and 104 history-

Table 1 The responsiveness of patients to diet and to provocation with histamine

	Total	Positive response	No response	
Response to diet				
Number of patients	157	72	85	
UAS7 days 0–7		23.6 ± 1.0	21.8 ± 0.8	
UAS7 days 25–31		10.4 ± 0.9	22.4 ± 0.9	
Reduction in UAS7 (%)		56% – $P < 0.0001$	–3% – $P = 0.38$	
Response to oral histamine	**Total**	**+ Erythema**	**+ Itch**	**+ Diarrhoea**
Weal response	27	14	15	1
Erythema	25		15	3
Itch	21			2
Diarrhoea	8			

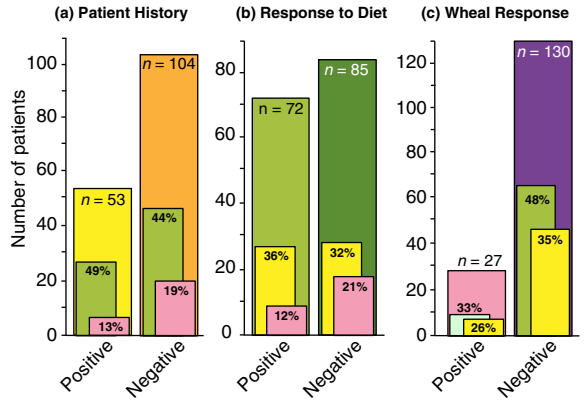

Figure 1 The coincidence of patient history, response to diet and a wheal response to each other. (a) The number of patients with a histamine-positive history is shown in the yellow column and the number with a histamine-negative history in the orange column. The light green bars show the percentage of patients within each group who had a positive response to diet, and the pink bars show the percentage of patients with a weal response to oral histamine challenge. (b) The number of patients with a positive response to diet is shown in the light green column and the number with a negative response in the darker green column. The yellow and pink bars show the percentage of patients within each group who had a histamine-positive history and a weal response to oral histamine challenge respectively. (c) The number of patients with a positive weal response to oral histamine provocation is shown in the pink column and the number with a negative weal response in the purple column. The yellow and pink bars show the percentage of patients within each group who had a histamine-positive history and positive response to diet respectively.

negative patients, the proportions of diet and histamine provocation weal-positive patients were not significantly different ($P = 0.766$ and 0.542 respectively). Second, the diet-positive and -negative groups contained similar proportions of history-positive ($P = 0.751$) and histamine provocation weal-positive patients ($P = 0.295$). Third, the histamine provocation weal-positive and -negative groups had similar rates of history-positive patients ($P = 0.665$) and diet-positive patients ($P = 0.437$). Finally, only 2 of the 157 patients were positive in all three domains.

Discussion

The clinically most important outcome of this study is that histamine intolerance is a relevant cause in only very few CSU patients and that patient history is not reliable. Only 17% of CSU patients showed a weal response to placebo-controlled histamine provocation. Most of these patients had not experienced urticarial responses to eating histamine-rich foods and most did not benefit from a histamine-free diet.

That the symptoms of 46% of the CSU patients included in this study were significantly improved after a histamine-free and pseudoallergen-low diet is consistent with response rates of 73% and 28% from previous reports.[2,15] Notably, benefit from this diet may be due to the avoidance of histamine, other pseudoallergens or both, or may be independent from the dietary effects of this measure altogether. The weaknesses of this study were that there was no control group on a 'normal' diet and the diet phase was not blinded so a placebo effect, however unlikely, cannot be excluded.

A further clinically relevant question raised was whether a history of histamine intolerance in CSU patients can predict a positive response to a histamine-free diet or oral histamine provocation. Clearly it does not. Although patients with histamine intolerance frequently have a positive history, i.e. signs and symptoms after eating histamine-rich foods,[3] this does not appear to be the case in CSU patients. In other words, CSU patients may or may not benefit from avoiding histamine in their diet, but this cannot be predicted based on their previous experience of tolerating or not tolerating histamine-rich foods. Likewise, although CSU patients may have their histamine intolerance confirmed by oral histamine provocation, this cannot be predicted by their history of not tolerating histamine-rich foods.

In conclusion, less than half of the 60 CSU patients with provocation-confirmed histamine intolerance showed urticarial responses after provocation, and less than 10% of these patients

had problems with histamine-rich foods in their daily lives or got better when avoiding histamine. Thus, CSU due to histamine intolerance appears to be rare and cannot be diagnosed based on the history. Avoidance diets that are low in pseudoallergens, as recommended by the EAACI/GA^{2}LEN/EDF/WAO urticaria guideline,[1] can improve urticaria activity, but in most patients who respond, this is probably not due to the absence of histamine in these diets.

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