

Management of chronic idiopathic urticaria by the identification and exclusion of dietary factors

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Summary

The role played by dietary chemical factors in the pathogenesis of chronic idiopathic urticaria (CIU) was assessed in seventy-six patients by challenge. Stable remission was first established by using an empirically established 'exclusion diet'. A diet modified to exclude those chemicals giving a positive response to challenge was demonstrated to be of therapeutic value for time periods of up to 18 months. Re-testing twelve patients at 12 months indicated that most patients positive to salicylate or benzoate challenge retained this pattern of reactivity.

Introduction

Chronic urticaria is a common disorder presenting as cutaneous weals caused by release of vasoactive mediators from mast cells within the dermis, occurring on a continuous or recurrent basis over prolonged periods of time. Release of histamine from mast cells reflects the net effect of several intra-cellular events, which in turn are influenced by the state of activation of membrane receptors. Thus chronic urticaria is a clinical syndrome, whereby any one of a variety of hormonal, immunological, or physical factors may be the major precipitant in a particular patient (Taffe, 1977). The majority of patients have no definable underlying disease or specific physical precipitants, and can be termed 'chronic idiopathic urticaria' (CIU). Recently a number of chemicals present in foods have been shown to precipitate acute exacerbations and claims have been made that diets constructed to exclude these factors may induce prolonged remission (Michaelsson & Juhlin, 1973; Doeglas, 1975; Warin, 1976). This prospective study of 76 patients with documented CIU provides further information on the role played by a variety of dietary factors in this disease, and demonstrates a successful and practical approach to the management of the disorder.

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Materials and methods

Patients

Seventy-six patients with CIU referred to the Allergy Clinic at Royal Prince Alfred Hospital have been studied. Diagnosis was established, according to the following criteria: (i) lesions present for at least 3 months; (ii) exclusion of patients with disease known to be complicated by urticaria, e.g. systemic lupus erythematosus, dysproteinacemias, thyrotoxicosis, vasculitis, infection, etc.; (iii) exclusion of the physical and cholinergic urticarias; (iv) exclusion of urticaria occurring as part of an allergic reaction to an identifiable antigen (usually acute).

Clinical details can be summarized: 58% were women; age range was 10–75 years, 87% had intermittent angioedema, 8% had unexplained arthralgia and 8% had asthma. ESR, C1 esterase inhibitor, C3, C4, and C50 values were normal, and cryoglobulins were not detected. Fifteen of forty-four (36%) patients had circulating immune complexes detected at some stage of disease, but no clear correlation with disease activity was noted. The immune complex assay was a modification of the CIq deviation test (Clancy *et al.*, 1979). Antinuclear antibody was positive in 7% and 21% were atopic (defined by having positive prick tests to a test batch of allergens), incidences similar to those within a normal population. All patients had taken antihistamines, and many had taken beta adrenergic stimulants with variable symptomatic improvement. Nineteen patients had taken corticosteroids at some stage, with little clinical value.

To gain some assessment of disease severity, the following clinical score was used; 0 = no urticaria; 1 = occasional urticaria (less than one episode each week); 2 = frequent urticaria (more than one episode each week); 3 = constant urticaria (i.e. urticaria present most days of the week; mild/moderate severity); 4 = constant-severe (as for 3 but more severe; often taking corticosteroids).

Design

Following diagnosis, an exclusion diet was prescribed for a 2–4 week period, during which time fifty-four patients came into complete remission and fifteen into partial remission. Drugs were discontinued, and the chemical challenges administered. Details of this diet have been described (Gibson & Clancy, 1978) and are summarized in the addendum. The test substances were encapsulated in clear gelatin. The order of testing and dosage level are given in Table 1.

Table 1. Order of testing and dosage level

Order of challenge	Challenge	Amount
1	Lactose	Placebo
2	Tartrazine	10 mg
3	Sodium benzoate	500 mg
4	4-OH benzoic acid	200 mg
5	Brewer's yeast	0.6 mg
6	Penicillin	250 mg
7	Acetyl salicylic acid	150 mg
8	Acetyl salicylic acid	300 mg

Each test substance was taken after remission was obtained. One substance was taken every second morning. The patient's food intake was charted, as was the nature and severity of symptoms. A positive result was recorded if urticaria or angioedema appeared within 24 hr of the challenge. Tests were not continued until lesions subsided (often 24-48 hr). On the basis of positive reactions, the diet was revised to restrict only those foods thought to contain chemicals causing reactions (Gibson & Clancy, 1978). Follow-up was at 1, 3, 6, 12 and 18 months. At 12 months some patients were re-challenged and diet revised accordingly.

Results

Exclusion diet

The severity of CIU on entry into this study is represented in Fig. 1. Assessment one month after beginning an exclusion diet can be seen in Fig. 1. Thus 65% of the patient

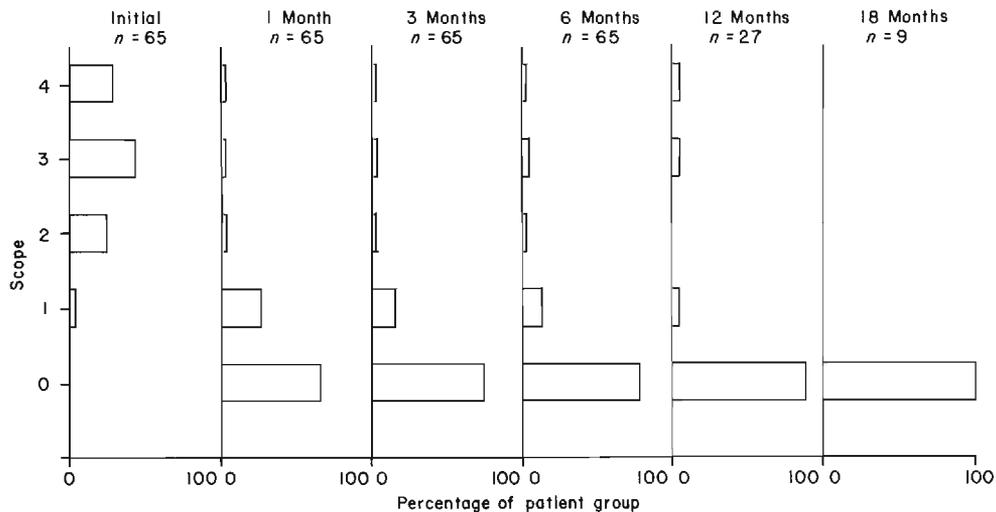


Fig. 1. Clinical state following modified exclusion diet for chronic idiopathic urticaria indicating prolonged remission in most patients.

group were in complete remission, a figure which had increased to 75% by 3 months. Assessment did not include episodes of urticaria that followed dietary indiscretion which were clearly identified as such by the patient. The percentage in complete remission increased with time, though only nine patients were followed for 18 months. Most patients (i.e. 90%) stabilized after being on the exclusion diet for several days to 2 weeks, though some required longer periods of time and careful dietetic assessment with much trial and error.

Statistical analysis of change in clinical score at different time periods is of doubtful value given the method of assessment of severity. However, if the null hypothesis is tested for the sampled populations having the same median value, it is highly probable that a shift has occurred with time (probability of identical median values < 0.005). The shift is clearly towards a lower score with time. In the absence of a double blind prospective study spontaneous clinical improvement is possible, though unlikely when

the exacerbating effect of dietary indiscretions and the re-challenges at 12 months are considered.

Challenge with test substances

Seventy-six patients fulfilled the diagnostic criteria for CIU. Seven refused the diet, and four were lost to follow up after challenge. The results are summarized in Table 2.

Table 2. Details of percentage reacting to challenge with test substances

Challenge	Percentage reacting
Lactose placebo	0
Salicylate (S)	54
Benzoate/benzoic acid (B)	34
Tartrazine (T)	26
Yeast (Y)	12
Penicillin (P)	18
S/B	17
S/T	16
S/B/T	4
B/T	12
S/P	12
B/P	8
T/P	4
P/Y	8
S/Y	7
B/Y	5
T/Y	4

Twelve patients agreed to re-challenge after remaining on the diet for 12 months. Each patient was in complete remission. One patient failed to respond to the initial challenge, and also gave no response at 12 months. Of four who initially responded to benzoate, three remained positive at 12 months. Of seven who responded initially to salicylate, five remained positive at 12 months. Of those initially reacting to tartrazine (three), penicillin (two), yeast (one), all were negative to re-challenge with these substances. One patient who reacted to benzoate alone initially, reacted to benzoate and salicylate on re-challenge.

Discussion

Because of the poor response of CIU to traditional drug therapy, we examined the clinical value of minimizing certain dietary factors, which have recently been incriminated in the pathogenesis of this disorder (Michaelsson & Juhlin, 1973; Doeglas, 1975; Warin, 1976). The test population was carefully defined to exclude symptomatic urticaria and specific disease was excluded on clinical and laboratory grounds. Of particular value in differentiating symptomatic urticaria from CIU was a negative antinuclear antibody, a normal ESR, absent cryoglobulins, and absence of vasculitis on skin biopsy when necessary.

Our approach to the identification of dietary chemicals which contribute to the

pathogenesis of CIU was similar to that of Waren & Smith (1976). An important difference in our protocol, however, was an attempt to establish a stable asymptomatic remission prior to challenge, with a diet constructed to exclude most of the test chemicals (Gibson & Clancy, 1978). Advantages of this approach include an increase in sensitivity to test substances through discontinuation of antihistamines, and a reduction of false positive responses from factors included in a normal diet. The negative response to lactose placebo in every patient in this study emphasizes the importance of control of background 'noise' and contrasts with the experience of other workers (Michaelsson & Juhlin, 1973; Doeglas, 1977). It must be recognized, however, that many of the decisions made in the dietary management of these patients are arbitrary and empirical through lack of knowledge of the exact quantities of the test chemicals in foods, and that any prescribed diet must be used only as a guideline, and cannot replace careful enquiry, trial and error. The value of experience through working with large numbers of patients with CIU cannot be overstated. Precise management awaits chemical analysis of common foods, when almost certainly other factors will be added to the challenge protocol.

The pattern of reactions to challenge was remarkably similar to that found by others (Champion *et al.*, 1969; James & Warin, 1970; Warin & Champion, 1974; Settupane *et al.*, 1976; Warin & Smith, 1976). The clinical response to diet modified according to the response to challenge, was significant improvement at time periods up to 18 months. Many patients noted that failure to keep to the established diet was followed by urticaria, while others found that they could gradually take foods which previously caused episodes of urticaria. Some were able to successfully return to their previous food intake, though 73% of patients re-tested after 12 months retained a positive response to challenge. Factors relevant to the precipitation of urticaria could not be predicted with confidence from the clinical history unless patients identified aspirin-containing drugs. The close positive correlation between challenge results and the subsequent clinical course (i.e. remission with modified diet and the response to re-challenge at 12 months) vindicated the empirically derived diets (which at least in the case of the low salicylate diet is largely confirmed by chemical analysis (A. Gibson, unpublished observations). The chronic and fluctuating natural history of CIU does not appear to be modified by dietary management (Warin & Smith, 1976).

The trigger for histamine release in CIU is not known, nor is the mechanism whereby salicylates, benzoates, tartrazine and other dietary factors modulate the mast cell release reaction. The non atopic status of most patients does not deny any IgE-mediated mechanism, an hypothesis which requires formal testing *in vitro* with hapten-host protein conjugates. Immune complexes were detected in one-third of the patients tested but their presence did not correlate with symptoms, dietary state, or challenge. Thus at this time there is no evidence to support antibody as a mechanism by which dietary factors promote mast cell secretion. A non-immunological mechanism which modulates mast cell membrane stability or intracellular cyclic nucleotide levels is a more attractive hypothesis to account for the correlation between dietary and clinical event.

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Addendum: Foods allowed in elimination diet

Meat: Lamb, chicken, beef, veal, turkey (N.B. corned beef not allowed).

Vegetables: Lettuce, carrots, parsley.

Fruit: Pears, fresh and canned.

Cereals: Matzo (biscuits) plain flour, semolina, rice noodles, rice vermicelli, rice, rice bubbles, San Remo spaghetti, Carrs water biscuits.

Fats: Oils, e.g. safflower, sunflower.

Sugars: Sugar, golden syrup, honey.

Miscellaneous: Malt vinegar, salt, pepper, gelatine.

Beverages: Coffee, pear nectar.

Soups: Home made soups using above ingredients.

Desserts: Home made using above ingredients.