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CLINICAL RESEARCH

Outcome of a Histamine-restricted Diet Based on Chart Audit

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Abstract

Purpose: *This is a report of the outcome of dietary management (histamine restriction) of 44 subjects referred to a food allergy clinic over a 12-month period for management of 'idiopathic' urticaria, angioedema and pruritus (U/A/P), because their symptoms had resisted previous treatment and because a preliminary study had shown potential response to such a diet in comparison with placebo. Additionally, the effect of this type of dietary management was reported on numerous other symptoms.*

Design: *Statistical evaluation of outcome based on clinical signs and symptoms.*

Materials and Methods: *Because the U/A/P symptoms of the subjects evaluated in the study were characteristic of a histamine mediator response, a histamine-restricted diet was implemented for a 4-week trial. By means of chart audit, symptoms which had been rated by subjects according to severity were compared at the beginning and the end of the trial period, as was the change in intake of antihistamine medication.*

Results: *The degree of improvement in symptoms varied, depending on the symptom reported and the gender and age of the subject. For U/A/P symptoms, 61.4% reported significant improvement, 18.2% reported 'some improvement', while 20.4% showed no improvement. Women (more prevalent) reported a greater degree of improvement than men. Of the additional symptoms, no-one reported improvement in atopic dermatitis or contact dermatitis (n = 4); 50% of subjects reported improvement in migraine headaches, while 50% reported no improvement (n = 10); 80% of subjects with gastrointestinal tract symptoms reported improvement (n = 9); 100% of subjects reporting 'panic attacks' as one of their additional problems (n = 3) reported complete remission of this symptom.*

Conclusions: *A randomized, double-blind controlled trial with an appropriate sample size would be required to ensure that the observed symptom relief in our subjects with recalcitrant idiopathic U/A/P is not due to bias or chance. Considering that a histamine-restricted diet has been beneficial in this uncontrolled pilot study, a time-limited trial on the diet, which poses no risk of nutritional deficiency, may be warranted for subjects exhibiting the type of resistant symptoms reported.*

Keywords: urticaria, angioedema, pruritus, tachycardia, panic attack, histamine intolerance, histamine-restricted diet.

INTRODUCTION

There are varying opinions on the significance of biogenic amines in non-immunologically mediated reactions to foods that may be termed 'food intolerance', in contrast to 'food

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allergy', a type I (IgE-mediated) hypersensitivity reaction, triggered by an allergen—an antigenic protein [1]. Food intolerance is usually mediated by small molecular weight chemical substances and biologically active components of foods [2]. Histamine is an important example of a biologically active component that can be found in many foods and beverages. Whereas high doses are toxic for all humans, individual tolerance is the important characteristic that determines reactivity to small quantities. Just about everyone who ingests pre-formed histamine from a contaminated food at a level of more than 2.7 mg kg^{-1} body weight will show symptoms of 'histamine poisoning' [3], but at lower concentrations only a few sensitive individuals will experience an adverse reaction. It is likely that differences in levels of tolerance are of genetic origin, but tolerance can be reduced by disease and medications [3].

Because histamine is the most important mediator responsible for the symptoms of 'classical allergy' in the type I (IgE-mediated) hypersensitivity reaction, it is difficult for clinicians to distinguish between reactions due to allergy and those resulting from histamine excess, as the symptoms are essentially the same in both cases. Typical symptoms of food allergy include urticaria, angioedema, rhinitis, asthma, headaches, oral allergy symptoms, and digestive tract complaints such as nausea, flatulence, abdominal cramps and diarrhoea [4]. Similar symptoms can result from 'histamine excess' in the absence of detectable allergen [2].

The determination of whether symptoms that arise after eating certain foods are caused by an immunologically mediated hypersensitivity reaction to an allergen (allergy) or a non-immunologically mediated response (intolerance) to histamine is difficult. No test designed to establish allergy or intolerance carried out on a patient (*in vivo*) or in the laboratory (*in vitro*) will of itself allow one to formulate the diagnosis with certainty [5]. The diagnostic accuracy of currently available tests is low, and for some tests there are no studies on diagnostic sensitivity and specificity. Therefore, the diagnosis of food allergy or food intolerance has to be based on observation of the patient's response after elimination of the suspect food, and confirmed by subsequent exposure to that food component [6].

It is important to determine the mechanism responsible for an adverse reaction to food because dietary management will depend on the identity of the food component responsible for triggering the response. In the case of IgE-mediated food allergy, the critical factor in the adverse reaction is the presence of the protein allergen; in the case of food intolerance, the adverse reaction depends not only on the presence of the problem food component, but also the amount of the food component ingested, and the sensitive person's efficiency in metabolizing it.

In the case of histamine intolerance, the production of excess histamine produces a person's symptoms. The excess may be due to the amount of histamine synthesized and released intrinsically (including that required for normal physiological processes as well as that released in an inflammatory or allergic response), the amount ingested from ancillary sources within the body (e.g. decarboxylation of histidine by the resident microflora from unabsorbed food material in the colon), and the amount ingested from extrinsic sources, as well as the efficiency of catabolic enzymes to reduce the excess within the body. Of these, the most easily manipulated factor is the amount of histamine in food. A decrease in dietary histamine, even though it can only partially reduce the total body histamine burden, can be an important strategy in the management of histamine intolerance.

METHOD

Rationale

For a number of years we have observed improvement in subjects referred to the Allergy Nutrition Clinic at Vancouver Hospital and Health Sciences Centre (ANC) with a diagnosis of idiopathic, chronic urticaria and angioedema after following the histamine-restricted diet

developed according to these parameters. A preliminary study indicated its possible effectiveness in comparison with a 'placebo' diet [7].

Selection of Subjects

Forty-four consecutive subjects referred to the ANC for dietary management within a 12-month period in 1997–1998 were entered into the study when the following criteria were met:

- Referred to the ANC by a physician for investigation of the role of diet in urticaria, angioedema and pruritus (U/A/P);
- Symptoms present for a minimum of 3 months;
- Age: older than 7 years, with no upper age limit;
- Causes such as parasite infestation, microbial and viral infections, autoimmune disease, or other pathology that could account for the U/A/P were ruled out by previous investigations;
- Skin test was negative for all food allergens tested, or had achieved no symptomatic improvement after strict avoidance of all skin test-positive foods;
- Absence of medications that could be involved in the aetiology of symptoms; essential medications for non-related conditions were continued during the trial period;
- Report of symptom status on at least one follow-up visit to the ANC after 4 weeks on the histamine-restricted diet.

Formulation of the Histamine-restricted Diet

Biogenic amines are catabolic products of amino acids and are a result of both animal and plant metabolism [8]. They are present in almost all foods in small quantities [2]. Large quantities result from microbial activities during ripening and rotting of foods, and during the manufacture of fermented foods such as cheese, wine, vinegar, fermented sausages, soy sauce, and sauerkraut [9–13]. The development of a 'low histamine diet' is a complicated task because so many factors determine the level of histamine in a food at the time of its consumption.

Some of these factors are:

- The level of microbial activity during the food's manufacture (e.g. the extent of 'ageing' of a cheese [9]; the degree of fermentation of a processed meat or sausage, or a fermented condiment such as soy sauce; the level of fermentation of an alcoholic beverage [13, 14]);
- The degree of microbial activity in stored meats and fish, especially intact, non-gutted fish and shellfish [11];
- The degree of ripeness of fruit [9];
- Amine development during pickling or curing in brine [15].

Level of Histamine in Foods and Beverages

A number of published reports provide information on the levels of histamine in commonly eaten foods [9]. However, it is difficult to define a 'safe' level and a 'toxic' level of histamine in food because people differ in their degree of tolerance. Nevertheless, it has been reported, and generally accepted, that histamine concentrations of 100–225 mg kg^{-1} represent a toxic level in foods and beverages [12, 16, 17]. A German databank, established as a resource for people with sensitivity to amines in foods and beverages [11], uses a level of 1 mg kg^{-1} as the threshold level between low histamine foods (< 1 mg histamine kg^{-1}) and high histamine foods (> 1 mg kg^{-1}). Reported levels of histamine in foods analyzed

by different methods vary significantly from laboratory to laboratory. It is conceivable that the discrepancies in values stem from a variety of sources, one of which seems to be the degree of ripeness of fruits and vegetables [18], as well as differences in methods of analysis [9].

Early studies of the levels of histamine and other amines in foods used thin-layer chromatography [19]. More recent research employs methods of overpressure-layer chromatography, high-performance liquid chromatography, and gas chromatography [8]. Probably the simplest method for the quantitative determination of biogenic amines in foods is chromatography on an amino acid analyzer [20]. Other methods include fluorometry and high-voltage electrophoresis [21]. The foods excluded from the histamine-restricted diet are those whose histamine content has been reported to be > 1 mg kg^{-1} by any method of analysis in readily accessible published data sources.

Restriction of 'Histamine-releasing' Foods

Several naturally occurring chemicals and food additives have been credited with the ability to release histamine in the body by non-immunologically mediated mechanisms that are for the most part incompletely understood, and have been popularly referred to as 'pseudo-allergic reactions' [3, 22]. Food additives that have been implicated as potential factors in the release of histamine and triggering urticaria and angioedema on occasion include: tartrazine and other azo dyes [8, 23], salicylates [24] and preservatives such as sulphites [25], benzoates [26–28], butylated hydroxyanisole (BHA) and butylated hydroxytoluene (BHT) [29, 30]. Some of these chemicals occur naturally in foods (e.g. benzoates [27, 31] and sulphites [25]). In order to reduce the possibility of histamine levels being increased by the action of these naturally occurring chemicals and food additives, they were all excluded from the diet.

Table 1 lists the restricted foods, beverages, and food additives. The subjects were supplied with extensive instructions on diets, individualized according to each person's lifestyle and tastes, that excluded the 'high histamine' foods and supplied complete balanced nutrition from alternative sources. The histamine-restricted diet was followed by each subject for 4 weeks.

Evaluation of Symptoms

Each subject's appraisal of the severity of their initial symptoms was recorded in the ANC chart on a five-point scale. After 4 weeks on the histamine-restricted diet, each subject provided the same type of evaluation of each of their symptoms, graded on a scale of 0 (absent) to 4 (extremely severe). Based on these reports, symptom changes were recorded as: 0, no change; $+1$, some improvement; $+2$, significant improvement; -1, some worsening; -2, significant worsening.

Evaluation of Compliance with Dietary Directives

Each subject was required to provide a diet and symptom chart on which they recorded their dietary intake for each meal and snack for the duration of the trial. Although this provided some indication of the extent to which the dietary guidelines were followed, people are notorious in providing the type of information that they assume the supervisor wants. No formal ranking of dietary compliance was therefore carried out beyond the subject's personal assessment of their degree of compliance. If ranking of compliance had been possible, a dose–response effect might have been demonstrated, i.e. the higher the compliance, the more positive the outcome.

TABLE 1. Histamine-restricted diet

The following foods were avoided during the 4-week trial elimination period:

Meat, poultry, fish

- Fish and shellfish whether fresh, frozen, smoked, or canned, if processing is unknown. (If the fish is freshly caught, gutted and cooked within 30 min it may be eaten.)
- Egg (a small quantity of cooked egg in a baked product such as pancakes, muffins, cakes is allowed).
- Processed, smoked and fermented meats such as luncheon meat, sausage, wiener, bologna, salami, pepperoni, smoked ham, cured bacon.

Milk and milk products

All fermented milk products, including:

- Cheese (any kind of fermented cheese such as Cheddar, Colby, Blue cheese, Brie, Camembert, Feta, Romano, etc.).
- Cheese products such as processed cheese, cheese slices, cheese spreads.
- Cottage cheese.
- Ricotta cheese.
- Yoghurt
- Buttermilk.
- Kefir.

Any milk or milk product that is NOT fermented is allowed.

Fruits

- Orange, grapefruit, lemon, lime.
- Cherries.
- Bananas.
- Strawberries.
- Apricots.
- Raspberries.
- Pineapple.
- Cranberries.
- Prunes.
- Loganberries.
- Dates.
- Raisins.
- Currants (fresh or dried).

Vegetables

- Tomatoes, tomato sauces, ketchup.
- Soy and soy products.
- Spinach.
- Red beans.
- Eggplant.
- Olives in vinegar or brine.
- Pumpkin.
- Avocados.
- Pickles, relishes and other foods containing vinegar.

Food additives

- Tartrazine and other artificial food colours.
- Preservatives: benzoates, sulphites, BHA, and BHT.

Many medications and vitamin pills contain these additives. Alternatives free from these preservatives should be substituted.

TABLE 1. *Continued*

Seasonings

- Cinnamon.
- Cloves.
- Anise.
- Nutmeg.
- Curry powder.
- Chilli powder.
- Vinegar.

Miscellaneous

- Fermented soy products (such as soy sauce, miso).
- Fermented foods (such as sauerkraut).
- Tea (regular or green).
- Chocolate, cocoa, and cola drinks.
- Alcoholic beverages of all types.
- 'De-alcoholized' beverages (e.g. beer, ale, wine, etc.).

RESULTS

Symptoms Reported by Subjects in the Study

All subjects reported symptoms of U/A/P, as required by the primary selection criteria. Additional symptoms reported by the subjects were:

- Skin: eczema, contact dermatitis;
- Respiratory tract: rhinitis, conjunctivitis, sinusitis, asthma;
- Gastrointestinal tract: abdominal bloating, abdominal pain, excessive flatulence;
- Central nervous system: migraine headache, other headache, depression, irritability, confusion;
- Other: tachycardia, 'panic attack', fatigue, joint and muscle pain.

(For the purposes of this paper, 'panic attack' as reported by our subjects refers to a feeling of overwhelming anxiety, increased heart rate, 'clamminess' of the skin, a feeling that 'I must get out of here', occasionally accompanied by brief episodes of 'blacking out' or frank syncope.)

Analysis of the Results

- Forty-four consecutive subjects with a primary diagnosis of U/A/P were selected, comprising 35 females and nine males.
- Thirty-six subjects reported additional symptoms, listed in Table 2. A total of 107 symptoms was reported by 44 subjects.
- The subjects ranged in age from 8 to 68 years, with a median age of 43.5 years.
- The subjects reported the duration of the U/A/P symptoms ranging from less than 1 year to 39 years, with a median duration of 4 years and a mean of 6.6 years [standard deviation (SD) = 8.4].

For the primary symptoms of U/A/P (44 subjects): 61.4% of the subjects reported significant improvement, 18.2% reported some improvement, and 20.4% reported no improvement (Table 3 and Figure 1).

Gender appeared to be a significant factor in the outcome of the diet on U/A/P symptoms. The females in this study reported a higher rate of 'significant improvement' compared with males (68.6% vs. 33.3%) (see Table 3 and Figure 2); however, the small number of male subjects may limit the significance of this result.

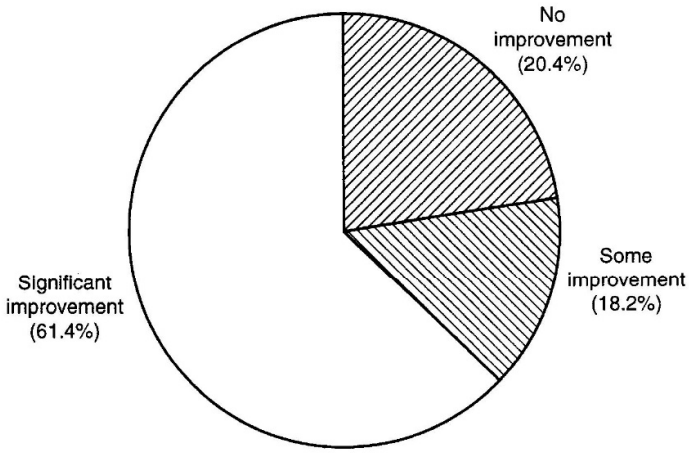

FIG. 1. Outcome of symptoms of urticaria/angioedema/pruritus after a histamine-restricted diet.

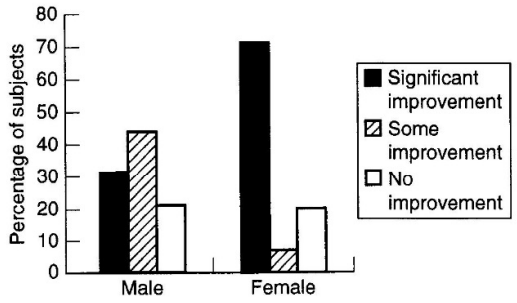

FIG. 2. Outcome of urticaria/angioedema/pruritus by gender.

The age at onset of U/A/P was available for 31 of the 44 subjects. The mean age at onset was 35.4 years (SD = 15.2; median = 32.0; range = 4–65 years).

The duration of U/A/P symptoms (computed as the interval between age and age at onset) was also available for 31 subjects. The mean duration was 6.6 years (SD = 8.4; median = 4.0), and the range was from less than 1 year to 39 years. Neither age at onset nor duration of symptoms appeared to be a significant predictor of improvement due to this diet (Table 4).

The outcome of the histamine-restricted diet appeared to be related to the type of symptom reported ($p = 0.013$) (Figure 3). The two subjects with eczema and both subjects with contact dermatitis showed no improvement. All three subjects with 'panic-like attacks' reported complete remission of symptoms. Eighty per cent of subjects with gastrointestinal complaints reported significant improvement (Table 5). The small numbers in these groups prohibited the authors from determining the statistical significance of these findings.

The female subjects appeared to respond significantly more to this diet than the males, when all symptoms were considered (Figure 4). However, the small number of male subjects may limit the significance of this result (Table 6).

The change in antihistamine medication for the control of U/A/P symptoms was assessed for 22 subjects who reported use of antihistamines. Fifteen subjects reported no antihistamine use, while use was unknown for the other seven subjects. Of the subjects using antihistamines, 59.1% (13/22) reported reduced use and 36.4% (8/22) reported no change

TABLE 2. Symptoms reported by subjects

Symptom category	Number of subjects with symptom ($n = 44$)	%
Urticaria/angioedema/pruritus	44	100
Gastrointestinal tract	12	27.3
Migraine headache and/or other headaches	13	29.5
Eczema	2	4.5
Contact dermatitis	2	4.5
Panic attack	3	6.8
Other symptoms	31	70.5

TABLE 3. Improvement in urticaria/angioedema/pruritus (U/A/P) resulting from diet, by gender ($n = 44$ subjects)

Outcome	Overall	Female ($n = 35$)	Male ($n = 9$)
Significant improvement	27 (61.4%)	24 (68.6%)	3 (33.3%)
Some improvement	8 (18.2%)	4 (11.4%)	4 (44.4%)
No improvement	9 (20.4%)	7 (20.0%)	2 (22.2%)

in use. One subject had increased use (Table 7). Statistical analysis was limited by the number of subjects.

DISCUSSION

The results reflect the experiences of 44 subjects (35 female; nine male) referred for investigation of the possibility that components of their diet might be contributing to the aetiology of a variety of symptoms ($n = 107$) that had not been ascribable to any other cause. After 4 weeks on a diet that excluded the foods known to contain high levels of histamine and those to which 'histamine-releasing' capability has been (historically) ascribed (Table 1):

- Twenty-seven subjects (61.4%) reported 'significant improvement' in the primary selection symptoms (U/A/P); eight more (18.2%) reported 'some improvement' in these symptoms (Figure 1).
- Gender might be a significant variable in such improvement, with women reporting a greater degree of improvement than men (Figure 2) (subject size too small for statistical analysis).
- Improvement in symptoms other than U/A/P was variable but interesting (Figure 3), but as these groups were small, no statistical conclusions could be drawn.
  - No subject reported improvement in atopic dermatitis (eczema) or contact dermatitis (two subjects in each category).
  - Fifty per cent of subjects with migraine headaches (five subjects) reported significant improvement, while another 50% (five subjects) reported no improvement in this symptom.
  - Improvement in symptoms of the gastrointestinal tract was reported to be 'significant' in 80% (eight subjects), while 10% (one subject) reported no improvement.
  - Perhaps the most surprising report of considerable improvement occurred in subjects with symptoms resembling anxiety or 'panic attacks', with tachycardia, lightheadedness, chest pain and, in one case, syncopal episodes. The three subjects who reported having panic attacks remained completely free from such symptoms while

TABLE 4. Improvement in urticaria/angioedema/pruritus (U/A/P) after diet, by age and duration ($n = 31$ subjects)

Outcome	No. of subjects	Age (mean ± SD)	Duration (mean ± SD)
Entire subject population	31	35.4 ± 15.2	6.6 ± 8.4
No improvement	6	41.3 ± 15.0	8.0 ± 7.3
Some improvement	6	39.5 ± 12.2	3.3 ± 3.1
Significant improvement	19	32.2 ± 15.9	7.2 ± 9.8
		$p = 0.34$	$p = 0.58$

p-values are not statistically significant.
SD, standard deviation.

TABLE 5. Improvement in all symptoms after diet ($n = 95$ symptoms)

	No. of subjects reporting outcome		No improvement		Some improvement		Significant improvement	
Symptom category	n	%	n	%	n	%	n	%
Urticaria/angioedema/pruritus	44	100	9	20.4	8	18.2	27	61.4
Gastrointestinal tract	10	22.7	1	10.0	1	10.0	8	80.0
Migraine and headache	10	22.7	5	50.0	0	0	5	50.0
Eczema	2	4.5	2	100	0	0	0	0
Contact dermatitis	2	4.5	2	100	0	0	0	0
Panic attack	3	6.8	0	0	0	0	3	100
Other	25	56.8	14	56.0	4	16.0	7	28.0

% = percentage of total subject population.

following the histamine-restricted diet, despite the fact that they had experienced the symptoms frequently (in one case daily) prior to commencing the diet. The size of this group precluded statistical analysis, but the finding is of interest.

Reasons for Excess Histamine

Biogenic amines play an essential role in maintaining the health of the body, both in defence against infection and trauma (in inflammation) and in physiological processes in various organ systems, such as the role of histamine in stimulating gastric secretions [31, 32]. However, when the same biogenic amines are present in excessive quantities they can induce symptoms. It is thought that the cause of histamine intolerance is most probably secondary to a defect in the catabolism of histamine [33].

In humans, enzymatic inactivation of histamine occurs through the operation of two enzymes, diamine oxidase (DAO) and histamine methyltransferase (HMT), which have different characteristics [34]. DAO occurs predominantly in the human intestinal mucosa as well as the placenta, kidney and thymus. HMT has a wider distribution, occurring in the stomach, lung, spleen, kidney, thymus, and particularly the brain [34]. Both enzymes may be intrinsically deficient [2] and can be inhibited by a variety of compounds [35], many of which are used as medications. Reduced DAO activity has been the subject of several investigations of conditions such as 'idiopathic' urticaria and angioedema in which an immunologically mediated hypersensitivity response has been ruled out [33, 36]. Laboratory findings of elevated plasma levels (>2 ng ml^{-1}) of histamine and reduced DAO activity (0.7 nkat l^{-1}) have been suggested as indicators of reduced histamine catabolism [2].

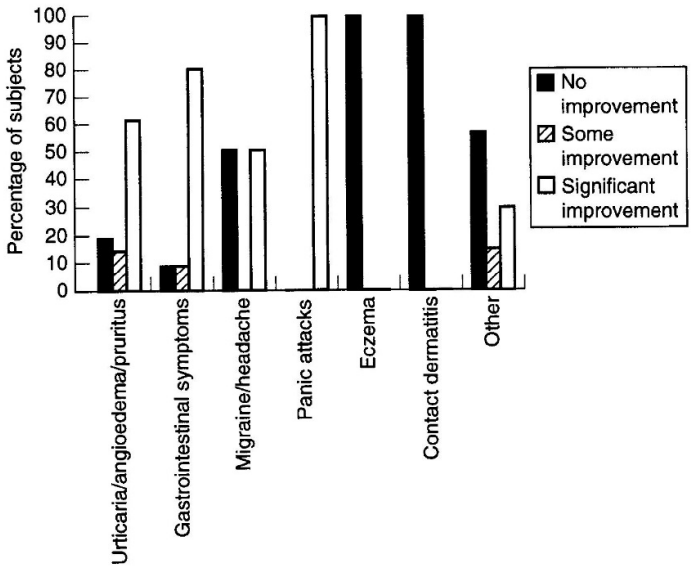

FIG. 3. Outcome of specific symptoms.

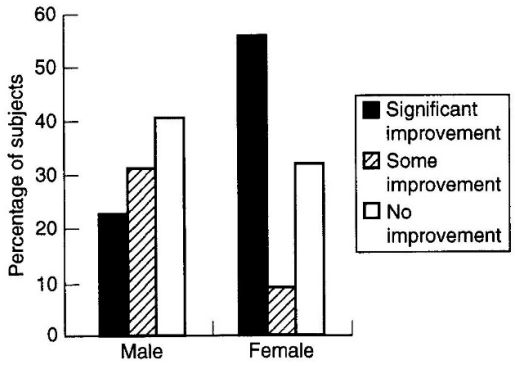

FIG. 4. Outcome of all symptoms by gender.

Sources of Excess Histamine

Histamine in excess of that required for essential physiological activities can arise from diverse sources. The most well known are the hypersensitivity reactions, in particular type I hypersensitivity (the classical immediate-onset allergic reaction), which involves mast cell degranulation triggered by antigen-specific IgE. However, there are several additional sources of histamine, both intrinsic and extrinsic, which increase the level of 'whole body histamine'. Such sources include production of histamine by the activity of micro-organisms on undigested food material in the large bowel [3], as well as in foods and beverages.

There are methods available for the measurement of the enzymatic function of DAO and HMT [33, 34, 36, 37] (most of which are tedious and fraught with procedural difficulties). In addition, it is possible, but difficult, to examine the resident microflora in the colon and estimate its potential capacity to decarboxylate histidine to histamine in undigested food materials [38, 39]. Such approaches might yield results that could suggest methods to

TABLE 6. Improvement in all symptoms after diet, by gender

Outcome	Female ($n = 35$)	Male ($n = 9$)	Total ($n = 44$)
No improvement	28 (33.7%)	5 (5.3%)	33 (34.7%)
Some improvement	8 (8.4%)	4 (4.2%)	12 (12.6%)
Significant improvement	47 (49.5%)	3 (3.1%)	50 (52.6%)

TABLE 7. Change in antihistamine medication used to control urticaria/angioedema/pruritus (U/A/P) symptoms by gender ($n = 22$ subjects)

Change in medication use	Female ($n = 17$)	Male ($n = 5$)	Total ($n = 22$)
Increase	0 (0%)	1 (20.0%)	1 (4.5%)
No change	6 (35.3%)	2 (40.0%)	8 (36.4%)
Decrease	11 (64.7%)	2 (40.0%)	13 (59.1%)

control both the source and metabolism of histamine, and future management of histamine intolerance might involve intervention at either of these points.

Although the potential sources of histamine in excess of the body's needs are numerous, in theory, the total level of histamine would be reduced by limiting the amount of histamine originating from extrinsic sources, namely food and drink, regardless of the efficiency of its catabolism by enzymes, the rate of its production by the resident microflora, and its release from mast cells. The present study examined the influence of extrinsic histamine in the diet as it contributes to the observed symptoms, and presumably to the total level of histamine in the body.

Histamine-restricted Diet

It is conceivable that the discrepancies in values stem from a variety of sources, one of which seems to be the degree of ripeness of fruits and vegetables [18], as well as differences in methods of analysis [9].

Study Outcomes

We selected subjects on the basis of a primary diagnosis of 'idiopathic' U/A/P made by their referring physicians. No further confirmation of this diagnosis was solicited. The purpose of this uncontrolled pilot study was to determine whether the selection of foods with a low content of histamine, and the exclusion of those previously suspected as capable of increasing the level of histamine in the body, would lead to remission of the symptoms that are probably mediated by its excess. The outcome suggests that this indeed appears to be the case, although the number of subjects in this study was small ($n = 44$) and the outcome must be considered accordingly.

A randomized, controlled trial of the histamine-restricted diet vs. a diet based on Canada's Food Guide would be a useful next step, particularly with a large enough sample size to minimize false-positive or false-negative results.

Subsequent research could involve the measurement of blood levels of histamine before, during, and after dietary histamine restriction, providing objective outcome measures to shed more light on the physiology involved in the association between dietary histamine and the clinical expression of its excess.

An ancillary outcome of this study was surprising: namely, the observation that three cases of tachycardia and 'anxiety' or 'panic attacks' responded to the histamine-restricted

diet. Possibly the hypotension and subsequent tachycardia could be associated with histamine-mediated vasodilatation, and a reduction in the level of 'whole body histamine', achieved by restriction of extrinsic sources of the amine, removed the cause. Further controlled trials of this observation are needed, as some cases of 'anxiety' and 'panic attacks' may be more effectively treated by reduction of histamine rather than behaviour modification. Interestingly, behaviour modification had apparently been attempted in our subjects and abandoned as ineffective.

The observation that migraine headaches were relieved in five of 10 of our subjects, but remained unchanged in an equal number, confirms previous observations in which diet seems to be effective in some cases of migraine, but makes little or no difference in others [37].

A similar observation was made for symptoms in the gastrointestinal tract [40].

Further questions remain to be answered: does the effectiveness of the diet used in this study depend on its low level of histamine, or are the symptoms reduced because of the exclusion of other factors, such as antigenic molecules that trigger a hypersensitivity reaction other than a type I, IgE-mediated response (e.g. a 'delayed' or 'hidden allergy') or a non-immunologically mediated food intolerance caused by amines other than histamine (tyramine, for example) [8], or other intolerance-triggering chemicals [22]? Further research will be needed to reveal the nature of the mechanisms responsible for food-associated symptoms.

CONCLUSIONS

A majority of the 44 subjects referred to the ANC with idiopathic U/A/P, as well as those with the additional symptoms reported here, which have resisted traditional management strategies, achieved relief of the symptoms, which are probably mediated by excess histamine, by following a low histamine diet. The subjects reporting symptomatic relief reported that the improvement in their quality of life has more than compensated for the adjustments required in their diet and lifestyle.

Until a more definitive randomized, controlled trial can be completed, others who suffer similarly may achieve at least some degree of relief by following the histamine-restricted diet. The foods eliminated from this type of diet can be easily replaced with others of equivalent nutrient value [41] and therefore there is negligible nutritional risk associated with a time-limited trial on this management programme. Because the response will be observed quite quickly, a period of 4 weeks on the diet will be sufficient for an individual to determine whether dietary manipulation will help in the management of their symptoms. Future research will eventually undoubtedly elucidate the precise reaction mechanisms responsible for the observed symptomatic responses.

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