

FOOD ALLERGY AND ADULT MIGRAINE: DOUBLE-BLIND AND MEDIATOR CONFIRMATION OF AN ALLERGIC ETIOLOGY

LYNDON E. MANSFIELD, MD;
T. RAY VAUGHAN, MD; STEPHEN F. WALLER, MD;
ROBERT W. HAVERLY, BS; and STANISLAUS TING, MD

Foods as a cause for migraine attacks were evaluated in 43 adults with recurrent migraine. Skin testing, elimination diets, double-blind challenges, and measurements of plasma histamine were performed. Thirteen subjects experienced 66% or greater reduction in headache frequency during a diet trial. Six subjects became headache free.

Eleven of 16 skin test-positive patients responded to diet manipulation, while only two of 27 skin test-negatives did ($P < .005$). Seven subjects agreed to double-blind challenges. In five of seven, at least one food provoked migraine. Placebo challenges did not provoke migraine. In three subjects, plasma histamine rose during migraine provoking challenges.

The relationship between food ingestion and migraine is based in part on allergic mechanism. Tests for IgE-specific food allergy appear helpful in selecting patients likely to benefit from diet therapy.

Introduction

A RELATIONSHIP between migraine headaches and allergic disease was proposed by Lesne and Richet in 1913.¹ Migraine was initially considered as one of the atopic diseases. A large number of reports linked food allergy with attacks of migraine.²⁻⁵ Controversy about food-induced migraine still exists among specialists in the field of allergy-immunology. Recent American textbooks of allergy and immunology do not discuss the relationship.^{6,7}

In the last decade, British investigators have explored the role of food allergy in the migraine syndrome. Grant, using a time-consuming therapeutic elimination diet trial, reported the diet led to freedom from migraine attacks in 51 of 60 patients.⁸ The other nine patients in

the study experienced a reduction in headache frequency. Other investigators have used food radioallergosorbent testing or RAST testing to predict successful diet therapy of migraine.⁹ During a more recent study of children with migraine, 78 of 88 patients recovered completely during a strict elimination diet. In 26 cases, the eliminated foods suspected of provoking attacks of migraine were confirmed by a double-blind challenge technique.¹⁰

In the present study, we sought to answer four distinct questions. (1) Is food allergy a common cause of adult migraine? (2) Is the food allergy skin test of use in predicting a therapeutic diet? (3) Would skin test-negative patients benefit from a moderately restrictive (wheat, egg, corn, milk free) diet? (4) Could evidence of mast cell activation be found during a migraine attack provoked by blind challenge?

Materials and Methods

Forty-three migraine patients with common or classic migraine, were referred to the Allergy-Immunology Service of William Beaumont Army Medical Center by a neurologist (S.W.). Criteria for the diagnosis of migraine were:

- (1) unilaterality,

From the Division of Immunology Allergy, Department of Medicine, Texas Tech University Health Sciences Center, 4800 Alberta Avenue, El Paso, Texas and The Allergy Immunology Service, William Beaumont Army Medical Center, El Paso, Texas.

The opinions or assertions contained herein are the private views of the authors and are not to be construed as official or as reflecting the views of the Department of Defense.

Reprint Request: Lyndon E. Mansfield, M.D., Chief, Division of Immunology Allergy Department of Medicine, Texas Tech University Health Sciences Center, 4800 Alberta Avenue, El Paso, Texas 79905.

FOOD ALLERGY & MIGRAINE — MANSFIELD ET AL

- (2) a throbbing or boring nature of the pain,
- (3) a temporal or occipital distribution,
- (4) radiation to involve the entire side of the head,
- (5) associated nausea,
- (6) visual blurring on the affected side, and
- (7) attenuation or complete amelioration with vasoconstrictor substance (Isometheptene, ergotamine).

Criteria 1, 2, 3, 5, 7, were present in all the subjects, with some variability in criteria 4 and 6.

There were 12 males and 31 females. Ages ranged from 17 to 62 years (mean 34 years). Headache duration was from 4 months to 48 years (mean 12 years). Headache frequency was from five per month to almost daily (mean 14.3/month).

Informed consent was obtained prior to the subjects entering the study. This project was approved by the Human Use Committee and the Clinical Investigation Committee of William Beaumont Army Medical Center.

Subjects were skin tested to a battery of 83 food allergens by the prick technique (Table 1). The testing extracts were purchased commercially from Greer Laboratories (Lenoir, NC). They were used as 1:20 wt/vol glycerinated extracts.

For the purposes of this study only, any food skin test whealing response greater than the negative control was considered positive, and the corresponding food eliminated from the subsequent trial diet. Codeine, a skin mast cell degranulating agent, was used as a positive control reagent¹; saline was used as a negative control reagent.

A diet trial was instituted for 1 month with all the

positive foods eliminated. If skin testing was negative, the volunteers were placed on a 1-month trial of a milk-, egg-, corn-, and wheat-free diet (Table 2). The subjects were instructed to record their diets, the frequency of headaches, and any medications used on a daily symptom diary sheet.

If the frequency of headaches did not decrease during the trial period, the subject left the study. The patients who improved, with at least a 66% reduction in headache frequency during the diet trial month compared with the previous 2 months, were asked to participate in double-blind food challenges in the clinic. One food or placebo challenge was performed each day using opaque white capsules with up to 8 g of food or placebo (sucrose). Three subjects agreed to have measurements of plasma histamine during both active food and placebo challenge tests. Plasma histamine was measured by a single enzyme isotopic method.¹¹

Results

Skin Testing

Forty-three patients were skin tested. Sixteen had a positive test to at least one food allergen (range 1 to 29 positive skin tests). Twenty-seven had negative food skin tests. All showed a positive wheal and flare skin response to codeine and a negative skin response to saline. A total of 13 subjects (11 of 16 food skin test positive group and two of 27 food skin test negative group) experienced a decrease in headache frequency. The mean number of headaches decreased from 14.3/month to 1.3/month. Six patients became free of headaches.

Table 1. Allergy Skin Tests—Foods

| | | | |
|--------------------|--------------------|----------------------|-----------------------|
| Animal Food | Leguminosae | Liliaceae | Rosaceae |
| beef | kidney bean | pineapple | strawberry |
| milk | lima bean | garlic | Compositae |
| chicken | string bean | onion | lettuce |
| egg, white | pea | asparagus | Miscellaneous |
| egg, whole | peanut | Umbelliferae | olive |
| lamb | soybean | carrot | cashew nut |
| pork | Solanaceae | caraway seeds | cloves |
| bacon | white potato | dill | nutmeg |
| Fish | chili pepper | Cucurbitaceae | black pepper |
| cod | tomato | squash (mixed) | vanilla |
| halibut | Pomaceae | cantaloupe | allspice |
| salmon | apple | watermelon | coffee |
| tuna | pear | Lauraceae | tea |
| trout | Rutaceae | cinnamon | sage |
| Mollusca | lemon | bay leaf | safflower |
| oyster | grapefruit | Juglandaceae | cardamon |
| clam | Drupaceae | English walnut | mushroom |
| Arthropods | almond | pecan | sweet potato |
| shrimp | plum | Sterculiaceae | banana |
| crab | peach | chocolate | ginger |
| lobster | apricot | coca cola | Chenopodiaceae |
| Raminae | Cruciferae | Palmaceae | spinach |
| barley | horseradish | coconut | bakers |
| corn | cabbage | | brewers |
| oats | mustard | | |
| rye | | | |
| wheat | | | |
| rice | | | |

FOOD ALLERGY & MIGRAINE — MANSFIELD ET AL

Table 2. Diet Free of Milk, Egg, Corn and Wheat

| | | |
|--------------------------|---|-------------|
| Tapioca (whole or pearl) | Squash | Water |
| White potato | Asparagus | |
| Sweet potato | Peas | Prunes |
| Lamb | String Beans | Peaches |
| Beef | Lima Beans | Pears |
| Chicken | Cane or beet sugar | Cranberries |
| Bacon | Salt | Apricots |
| Soy beans | Gelatin, plain | |
| Soy bean sprouts | Maple syrup or syrup made with cane sugar flavored with maple | |
| Lettuce | Vanilla extract | |
| Spinach | Crisco or spry, any vegetable shortening except oleomargarine | |
| Chard | | |
| Carrots | | |
| Beets | | |
| Artichoke | | |

Table 3. Foods Provoking Migraine and Confirmed by Double-Blind Challenge

| Patient | Positive Food Skin Test | Foods |
|----------|---|---------------|
| 1. S. B. | Cinnamon Cantaloupe Rye | Cinnamon |
| 2. M. N. | Halibut Coca Cola Allspice Coffee Nutmeg | Coca Cola |
| 3. L. P. | Wheat Salmon | Wheat |
| 4. R. N. | Pea Peanut | Pea Peanut |
| 5. P. E. | Pineapple Shrimp | None |
| 6. C. P. | Orange Squash Cantaloupe Grapefruit Horseradish | None |
| 7. C. F. | Corn Wheat | Corn Wheat |

Double-Blind Food Challenges

Seven subjects agreed to double-blind food challenge testing in the clinic. In five of the seven patients, we could confirm by double-blind challenge techniques that a food or foods identified by positive skin test provoked an attack of migraine. In several patients the positive challenge was repeated more than once. In one patient, four challenges to the same food (cinnamon) were positive, while four placebo challenges were negative. None of the placebo challenges provoked migraine attack (Table 3).

Measurement of Plasma Histamine

Three subjects agreed to repeat challenge with placebo and a proven migraine provoking food so that plasma histamine levels could be measured during the tests. All three subjects completed the active challenge

and two completed a placebo challenge. The third subject was unable to be challenged again.

The active food again produced migraine attacks in all three blinded subjects. Once again there was no response to placebo in the two subjects. Plasma histamine rose during the active challenges, but not during the placebo challenges (Table 4).

Discussion

In 1983 Egger and co-workers reported 78 of 88 children with migraine headaches became asymptomatic during a strict elimination diet.¹⁰ Additionally, these investigators were able to confirm that food provoked migraine in 26 children, (60%) in a double-blind fashion.¹⁰ This is quite similar to the 71% confirmation rate in the double-blind phase of our study.

The overall open trial improvement in our study was 30% in contrast to 88% in the pediatric study. This difference may reflect the different age groups that were studied. Food allergy appears to be a more frequent clinical problem in children. Another factor could be the less rigorous basic elimination diet we used compared with the other study. The amount of the challenge food may have influenced the observed difference. Many of the children received a portion equivalent of up to 120 g dried weight of foods. Some of our subjects tolerated a 2-g food challenge, but developed headaches at 8 g. The decision to stop at 8 g was based on previous work.¹² Clinical observations have suggested that a dose response relationship exists for food allergy reactions. It is now our opinion that real life equivalent challenges may offer a better model of natural exposure and bring greater insight into what happens in patients.

The number of subjects who underwent repeat challenge to the same food was small. But, on each challenge the results were the same, the food provoked migraine. The placebo caused no response.

These same three patients had elevations of plasma histamine during a migraine provoking blind food challenge. As far as we know, these are the first subjects in whom such evidence of mast cell mediator release during a migraine attack has been measured.

Besides histamine with its vasodilating properties, other mast cell mediators could participate in the pathogenesis of migraine. Further studies will be required to address the role, if any, of these other mast cell products. Also, the number of patients studied who have elevations in plasma histamine during a provoked

Table 4. Plasma Histamine Changes During Challenges

| Subject No. | Baseline | | Peak | |
|-------------|----------|---------|--------|---------|
| | Active | Placebo | Active | Placebo |
| 1 | 400 | 300 | 700 | 400 |
| 2 | 400 | 600 | 2,200 | 700 |
| 3 | 2,500 | N.D. | 11,600 | N.D. |

* Histamine in pg/mL; N.D. = not done; all active challenges provoked migraine; placebo challenges no migraine. High levels for subject #3 confirmed by two methods.

FOOD ALLERGY & MIGRAINE—MANSFIELD ET AL

attack needs to be increased to confirm our observations.

In spite of the need for further study, we believe that immunologic food reactions mediated by IgE should be considered in the clinical evaluation of common and classical migraine in adults as well as children. Tests for IgE-specific food antibodies can aid in selecting those patients most likely to benefit from a diet manipulation, however, these tests may not define all relevant foods. In patients with chronic recurrent migraine, evaluation of the role of foods in causing their disease appears a worthwhile undertaking.

References

1. Lesne, E., Richet C: Anaphylactic alimentaire aux œufs. *Arch Mal Enfants* 1913;16:81.
2. Brown TR: Role of diet in etiology and treatment of migraine and other types of headache. *J Am Med Assoc* 1921;29:1396.
3. Vaughan WT: Allergic migraine. *J Am Med Assoc* 1927;88:1383.
4. Eyermann CH: Allergic headache. *J Allergy* 1931;2:106.
5. Unger AH, Unger L: Migraine is an allergic disease. *J Allergy* 1952;23:429.
6. Golbert TM: Food allergy and immunologic diseases of the gastrointestinal tract, in Patterson Roy (ed): *Allergic Diseases*: *Diagnosis & Management*, ed 3 Philadelphia, J. B. Lippencott, 1980, pp 409-439.
7. Bock SA, May CD: Adverse reactions to food caused by sensitivity, in E. Middleton, Jr., Reed CE, Ellis EF (eds): *Allergy: Principles and Practice* St. Louis, C. V. Mosby Co, 1983, pp 1415-1427.
8. Grant ECG: Food allergies and migraine. *Lancet* 1979;2:966-968.
9. Monro J, Carini C, Brostoff J, et al: Food allergy in migraine: Study of dietary exclusion and RAST. *Lancet* 1980;2:1.
10. Egger J, Wil J, Carter CM, et al: Is migraine food allergy? A double-blind controlled trial of oligoantigenic diet treatment. *Lancet* 1983;2:865.
11. Dyer T, Waven K, Merlin S, et al: Measurements of plasma histamine: description of an improved method and normal values. *J Allergy Clin Immunol* 1982;70:82.
12. May CD, Block SA: A modern clinical approach to food hypersensitivity. *Allergy* 1978;33:166.

Requests for reprints should be addressed to:

Lyndon E. Mansfield, MD
Chief, Division of Immunology
Allergy Department of Medicine
Texas Tech University Health Sciences Center
4800 Alberta Avenue
El Paso, TX 79905

MAN'S TASK IN LIFE

"To be honest, to be kind, to earn a little and to spend a little less, to make upon the whole a family happier for his presence, to renounce when that shall become necessary and not be embittered, to keep a few friends but these without capitulation—above all, on the same grim condition, to keep friends with himself—here is a task for all that a man has of fortitude and delicacy. He has an ambitious soul who would ask more . . ."

Robert Louis Stevenson
The Noble Tasks