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ORIGINAL ARTICLE

A Prospective Audit of Food Intolerance among Migraine Patients in Primary Care Clinical Practice

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SUMMARY

This prospective audit was set up to investigate whether migraine sufferers have evidence of IgG-based food intolerances and whether their condition can be improved by the withdrawal from the diet of specific foods identified by intolerance testing. Migraine patients were recruited from primary care practices and a blood sample was taken. Enzyme-linked immunosorbent assays (ELISA) were conducted on the blood samples to detect food-specific IgG in the serum. Patients identified with food intolerances were encouraged to alter their diets to eliminate appropriate foods and were followed up for a 2-month period. Endpoints included identification of the specific foods that the patients were intolerant to, assessing the proportion of patients who altered their diet and the benefit obtained by these patients at 1 and 2 months. Patients reported the level of benefit on a 6-point scale, where 0 = no benefit and 5 = high benefit. Sixty one patients took part in the audit and 39 completed 2 months of investigation. The mean number of foods identified in the IgG test was 5.3 for all participants and 4.7 for those successfully altering their diet. About 90% of patients changed their diet to a greater or lesser extent following the identification of possible food intolerances. A marked proportion of the migraine patients benefited from the dietary intervention, approximately 30% and 40% reporting considerable benefit at 1 and 2 months, respectively. Also, over 60% of patients who reintroduced the suspect foods back into their diets reported the return of their migraine symptoms. This investigation demonstrated that food intolerances mediated via IgG may be associated with migraine and that changing the diet to eradicate specific foods may be a potentially effective treatment for migraine. Further clinical studies are warranted in this area.

Introduction

Dietary components are frequently proposed as precipitating factors for migraine, particularly in children and adolescents[1,2]. Many different foods have been implicated as potential triggers for migraine attacks, including chocolate, cheese, red wine and many others[3]. However, evidence for this interaction is mostly anecdotal and based on patient reports[4]. Open studies indicated that low-fat[5] and high carbohydrate[6] diets could lead to improvements in migraine frequency and/or severity. In contrast, no controlled study has confirmed the incidence of food-evoked migraine attacks. A controlled study with chocolate failed to show that it provoked migraine attacks[7]. An alternative concept of the relationship of food with migraine is that food cravings occur during the prodrome phase; the food intake thus being a consequence of the attack rather than a cause of it[8].

Migraine may be precipitated by food via chemical or immunological mechanisms. Dietary components may affect phases of the migraine process by influencing release of serotonin and noradrenaline, causing vasoconstriction or vasodilatation, or by direct stimulation of trigeminal ganglia, brainstem and cortical neuronal pathways[1]. Immunological reactions may be mediated by Immunoglobulin E (IgE [classical food allergies occurring immediately after eating]) or, more controversially, by Immunoglobulin G (IgG [food intolerance involving a delayed allergic reaction 2–120 hours after eating]). Available evidence indicates that an IgE mechanism is relatively unimportant in food-induced migraine[9] and a review of the clinical literature established no clear evidence of an immune dysfunction in migraine sufferers[10]. However, the role of a putative IgG mechanism is presently unknown.

The usual way to treat food intolerance is by food elimination and re-challenge procedures, which are imprecise, lengthy and inefficient. As a more efficient alternative to this approach, an enzyme-linked immunosorbent assay (ELISA) test to a panel of 113 food allergen extracts has been developed (YORKTEST Laboratories Ltd [YTL], York, UK). This detects raised food-specific IgG in the serum of people with one or more, usually chronic, conditions. Patients with raised IgG levels to specific foods are advised to remove these from their diets and their progress is monitored with a series of questionnaires. An independent audit of patients treated in this way between February 1998 and August 1999 showed that approximately 50% of all patients reported a high or relatively high response to dietary therapy, based on their levels of food-specific IgGs[11]. A randomised, controlled clinical trial has demonstrated beneficial effects of this form of dietary therapy on symptom relief for irritable bowel syndrome[12].

The present audit was set up to investigate whether migraine sufferers have evidence of IgG-based food intolerances and whether their condition can be improved by the withdrawal from the diet of specific foods identified by intolerance testing.

Patients and Methods

Patients

Established adult migraine patients (age > 18 years) were recruited from primary care clinical practices by their GPs. Patients were required to have high-impact headaches. Patients were diagnosed with episodic migraine (≤ 15 days of headache per month) or chronic migraine (> 15 days of headache per month), according to the GP's usual practices. All patients provided their written informed consent to take part in the audit.

Study Design

This prospective audit investigated whether migraine patients identified in primary care clinical practice exhibited food intolerances measured as elevated IgG levels to specific foods. The audit also investigated the effect of withdrawing foods associated with high IgG levels on patients' migraine attacks over a 2-month period.

Primary care physicians were briefed on the rationale and objectives of the audit at a meeting of the UK charity Migraine in Primary Care Advisors (MIPCA) and agreed to participate. Each physician recruited up to 20 migraine patients and provided them with information about the audit. Before entering the study, all patients completed a baseline questionnaire to record demography and allergy history and a Headache Impact Test (HIT-6[13]) questionnaire to record headache severity.

Patients who completed the initial questionnaires were sent a validated blood testing kit by YTL. Patients took a blood sample by skin prick as detailed in the leaflet enclosed with the testing kit and returned the kit to YTL by mail. The blood samples were processed by YTL on receipt of the questionnaires and blood kit. ELISA tests on blood samples were used to detect food-specific IgG in the serum of the blood samples. Results of the ELISA tests were sent directly to the patients by YTL, together with a guidebook on food intolerances and their treatment[14].

Patients were free to change their diets to eliminate specific foods identified by the ELISA tests as possibly causing intolerance, either on their own initiative or after consultation with their GP or other healthcare professional. Patients had access by telephone to a

professional dietitian to help them with any dietary alterations that they wished to implement. Follow-up questionnaires were sent to patients after 1 and 2 months to monitor their progress (investigation period).

Study Endpoints and Statistical Analyses

The main study endpoints were:

- Demographic data on the patient population, and details of their allergy and headache histories, analysed as descriptive statistics.
- Identification of the specific foods to which the patients could be intolerant, identified from the ELISA tests of IgG levels and analysed as descriptive statistics.
- The proportion of patients who altered their diet due to their ELISA test results, analysed as descriptive statistics.
- The benefit obtained at 1 and 2 months by the patients who altered their diet compared with the situation before diet alteration, analysed as descriptive statistics. Patients reported their level of benefit on a 6-point scale, where 0 = no benefit and 5 = high benefit.

Results

Patient Disposition

Sixty-one patients from six UK GP practices (range 1–17 per centre) were recruited into the audit and completed baseline assessments. In the investigation period, 46 patients (75.4%) continued in the study to 1 month and 39 (63.9%) to 2 months.

Baseline Demography and Headache Severity

Table 1 shows the demography of the patients who took part in the study. The average age was 45.2 years (range 21–68) and most patients (80%) were women. The majority of patients (78.0%) were in full-time education or employment. In examining the allergy history, 15 patients (24.6%) were aware of foods they felt they were allergic to, 42 (68.9%) were in contact with pets, 12 (20.0%) were in contact with chemicals or occupational dust, 52 (86.7%) were currently taking medication and 21 (34.4%) knew about medications they felt they were allergic to. Fifteen patients (24.6%) were current smokers and 18 (29.5%) had given up smoking. Forty three patients (72.9%) drank alcohol but only eight drank over seven units per week and only one drank more than 14 units per week.

Most patients had suffered from headache for a considerable time; 64% for ≥ 10 years, 20% for 5–10 years and 16% for < 5 years. Patients were severely affected by their headaches (Table 2). Eighty two per cent 'very often' or 'always' had severe pain, while 67% were 'very often' or 'always' limited in their usual activities during their headaches. Between 87% and 90% of patients were too tired to work, felt irritation and suffered from lack of concentration at least sometimes during their attacks. Patients reported a mean of 10.1 symptoms (range 1–24) associated with their headaches. Over 80% of patients reported that their headaches interfered with sleep, leisure and overall comfort. The mean weighted HIT score at baseline was 64.9 (range 48–78), corresponding to severe impact[13].

Table 1. *Baseline demography (n = 61)*

Gender	Male	12	20.0%
	Female	48	80.0%
Age group	Under 30	10	16.7%
	30 to 39	9	15.0%
	40 to 49	14	23.3%
	50 to 59	21	35.0%
	60 and over	6	10.0%
Employment status	Retired	3	5.1%
	Sick/disabled	4	6.8%
	Housewife	3	5.1%
	Part time	2	3.4%
	Full time skilled	25	42.4%
	Full time semi-skilled	17	28.8%
	Full time unskilled	2	3.4%
	Student	2	3.4%
	Unemployed	1	1.7%

Table 2. *Severity of patients' headaches: pain intensity, impact on daily activities and mood alterations*

Headache severity	Proportion of patients (%)				
	Never	Rarely	Sometimes	Very often	Always
Severe pain	2	0	16	61	21
Limit to usual activities	0	2	31	51	16
Desire to lie down	2	0	18	41	39
Too tired to work	5	8	51	31	5
Irritation	5	7	33	39	16
Lack of concentration	3	7	38	40	12

Identification of Food Intolerances

Food intolerances identified by IgG testing were analysed for the 61 patients who took part in the study and for the 39 who completed the 2 months of investigation. In the total study population, 60 of 61 patients (98.4%) had reactions to a total of 48 different foods, with an average of 5.3 (range 0–17) reactions per patient. In the patients who completed 2 months, 38 of 39 patients (97.4%) had reactions to a total of 36 different foods, with an average of 4.7 (range 0–17) reactions per patient. Table 3 shows the distribution of food intolerances in these two populations. The most frequently reported intolerances (in over 10% of patients in either population) were to cow's milk, yeast, egg white, egg yolk, wheat, gluten (gliadin), corn, cashew nuts, mollusc mix, brazil nut, cranberry and garlic (Table 3), and were similar in prevalence in the two populations.

Table 3. *Food intolerances in the audit population: number and proportion of patients with a positive ELISA test to IgG from various foodstuffs*

Food	Positive ELISA test (*n* [%])	
	Whole study population (*n* = 61)	Patients completing 2 months (*n* = 39)
Cow's milk	52 (85.2%)	34 (87.2%)
Yeast	37 (60.7%)	22 (56.4%)
Egg white	34 (55.7%)	23 (59.0%)
Egg yolk	20 (32.8%)	13 (33.3%)
Wheat	19 (31.1%)	12 (30.8%)
Gliadin	16 (26.2%)	10 (25.6%)
Corn	15 (24.6%)	8 (20.5%)
Cashew	12 (19.7%)	7 (17.9%)
Mollusc mix	10 (16.4%)	3 (7.7%)
Brazil nut	9 (14.8%)	6 (15.4%)
Cranberry	7 (11.5%)	5 (12.8%)
Garlic	5 (8.2%)	4 (10.3%)
Beef	3 (4.9%)	2 (5.1%)
Pork	3 (4.9%)	1 (2.6%)
Ginger	3 (4.9%)	2 (5.1%)
Buckwheat	4 (6.6%)	1 (2.6%)
Crustacean mix	5 (8.2%)	1 (2.6%)
Rye	2 (3.3%)	2 (5.1%)
Millet	3 (4.9%)	2 (5.1%)
Rice	1 (1.6%)	1 (2.6%)
Soya bean	5 (8.2%)	3 (7.7%)
Hazelnut	4 (6.6%)	3 (7.7%)
Mustard seed	1 (1.6%)	1 (2.6%)
Salmon/trout	2 (3.3%)	1 (2.6%)
Plaice/sole	3 (4.9%)	1 (2.6%)
Peanut	3 (4.9%)	2 (5.1%)
Chicken	3 (4.9%)	1 (2.6%)
Lentils	3 (4.9%)	1 (2.6%)
Pea	2 (3.3%)	1 (2.6%)
Almond	5 (8.2%)	3 (7.7%)
Cola nut	3 (4.9%)	1 (2.6%)
Duck	1 (1.6%)	0
Lamb	3 (4.9%)	1 (2.6%)
Turkey	2 (3.3%)	0
White fish	3 (4.9%)	1 (2.6%)
Kiwi	4 (6.6%)	2 (5.1%)
Pineapple	2 (3.3%)	0
Sunflower seed	2 (3.3%)	0
Oat	2 (3.3%)	0
Haricot bean	3 (4.9%)	2 (5.1%)
Coconut	1 (1.6%)	1 (2.6%)
Tea	1 (1.6%)	0
Carrot	1 (1.6%)	0
Barley	1 (1.6%)	0
Tuna	1 (1.6%)	0
Sesame seed	1 (1.6%)	0
Coffee	1 (1.6%)	0
Avocado	1 (1.6%)	0

Proportion of Patients who Altered their Diets

Of the 46 patients who returned the questionnaire after 1 month of investigation, 41 (89.1%) patients changed their diets to eliminate foods identified by the IgG testing and 5 (10.9%) did not. Of those who changed their diet, 19 (46.3%) reported that they altered their diets a lot and 22 (53.7%) reported they had made a 'reasonable attempt' to avoid the specified foods.

Of the 39 patients who returned the questionnaire after 2 months of investigation, 22 (56.4%) reported that they altered their diets a lot and 13 (33.3%) reported they had made a 'reasonable attempt' to avoid the specified foods. Two patients reported that they did not change their diet at all.

Benefit Obtained from Changing Diets

Figures 1 and 2 show the level of benefit reported by patients after 1 and 2 months, respectively, using the 6-point scale (0 = no benefit and 5 = high benefit). After 1 month, 27.5% of patients reported considerable benefit (scoring 4 or 5), while 30.0% reported little or no benefit (scoring 0 or 1). Of 18 patients who had retried foods they had stopped taking, five (27.8%) reported a strong return of migraine symptoms and seven (38.9%) a slight return. After 2 months, 38.2% of patients reported considerable benefit (scoring 4 or 5), while 32.4% reported little or no benefit (scoring 0 or 1). Of 26 patients who had retried foods they had stopped taking, seven (26.9%) reported a strong return of migraine symptoms and 11 (42.3%) a slight return.

A limited *post hoc* analysis was conducted to investigate the factors possibly associated with benefit. Of the 13 patients who reported considerable benefit from dieting after 2 months, nine (69.2%) said they had dieted strictly after 1 month and 12 (92.3%) after 2 months. Of the 11 patients who reported little or no benefit after 2 months, only two (18.2%) had dieted strictly after 1 month and five (45.5%) after 2 months. Compared to those who did not benefit, the patients who benefited were more likely to have suffered from bloating and sleep deprivation and to have never smoked (although all patients had given up at least 10 years previously). Those who reported no benefit from dieting were more likely to be trying other remedies as well, including avoiding chocolate and taking sumatriptan and homeopathic remedies. However, none of the above differences was testable for statistical significance due to the small number of patients involved.

Discussion

To our knowledge, this is the first investigation of possible IgG-mediated food intolerances in migraine patients. The patients who took part were all severely affected by their migraine, reporting high levels of pain and impact on their everyday activities. This is a group of patients who are typically poorly managed in primary care[15] and for whom new management initiatives would be welcome.

Almost all patients had multiple food intolerances in this investigation, identified as positive food-specific IgG test results. Typically, individuals were positive to at least one of cow's milk, egg and yeast, together with a small number of more individual reactions. These results are similar to those reported for other conditions[11,12]. Of the patients who took part in the investigation, about 90% changed their diet to a greater or lesser extent at both 1 and 2 months.

A marked proportion of the migraine patients benefited from dietary intervention by cutting out foods for which they had an elevated IgG level. Approximately 30% and 40% reported considerable benefit at 1 and 2 months, respectively. Reinforcing this is the fact that over 60% of patients who re-introduced the suspect foods back into their diets reported the return of their migraine symptoms. These results are encouraging and indicate that changing diet to counteract food intoler-

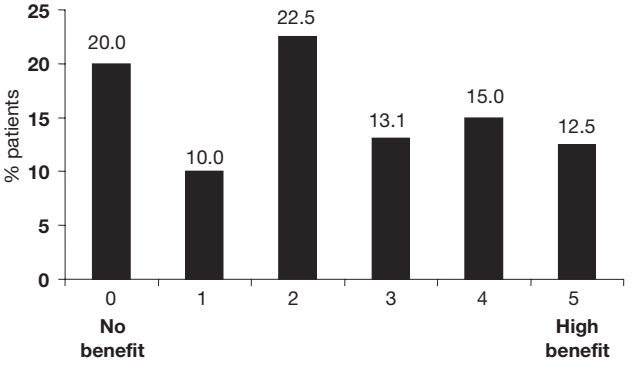

Figure 1. *Benefit of the diet after 1 month of the investigation: proportion of patients reporting their level of benefit on a 6-point scale, where 0 = no benefit and 5 = high benefit*

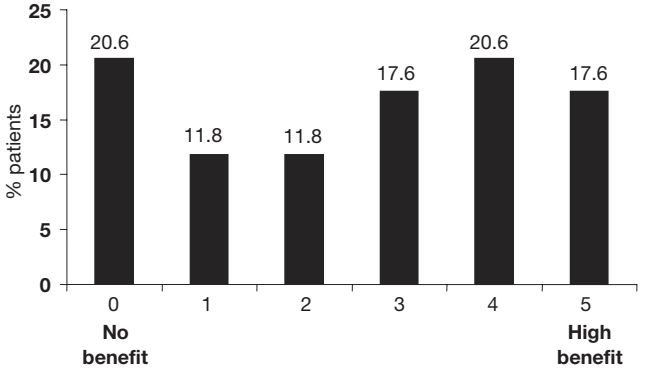

Figure 2. *Benefit of the diet after 2 months of the investigation: proportion of patients reporting their level of benefit on a 6-point scale, where 0 = no benefit and 5 = high benefit*

ances may be an effective treatment for at least some migraine sufferers.

However, it is not yet possible to recommend this approach for general clinical use. This investigation was a small audit to establish a possible relationship between food intolerances and migraine. In this it was successful, although benefits experienced by patients may have been due (in part or in whole) to a placebo effect. There remains a series of questions that need to be answered before we have proof of this concept:

- Do migraine sufferers differ from unaffected people or people with other disorders in the pattern of IgG that circulates?
- Do symptomatic reports of food intolerance correlate with the IgG data?
- Are migraine sufferers able to self-identify food intolerances?
- Does allergen avoidance lead to an improvement in migraine and can this be confirmed by re-challenge?

We suggest two follow-up studies that may answer these questions. Whether migraine patients differ from the general population and whether self-reported allergies correlate with food intolerances in migraine sufferers can be examined in a blinded study investigating the pattern of IgG-related food intolerances in migraine patients (with and without a history of allergy) and matched healthy controls without migraine. A small placebo-controlled study can then be used to study the effect of diet alteration on migraine symptoms. The study requires a re-challenge phase, and robust, validated endpoints, over a 3-month evaluation time.

In conclusion, this pilot audit demonstrated that migraine attacks may be related to food intolerances mediated via IgG and that changing the diet to eradicate specific foods may be a potentially effective treatment for migraine. Further clinical studies are required to confirm these findings and examine the clinical importance of this treatment approach.

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