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IS MIGRAINE FOOD ALLERGY?

A Double-blind Controlled Trial of Oligoantigenic Diet Treatment

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Summary 93% of 88 children with severe frequent migraine recovered on oligoantigenic diets; the causative foods were identified by sequential reintroduction, and the role of the foods provoking migraine was established by a double-blind controlled trial in 40 of the children. Most patients responded to several foods. Many foods were involved, suggesting an allergic rather than an idiosyncratic (metabolic) pathogenesis. Associated symptoms which improved in addition to headache included abdominal pain, behaviour disorder, fits, asthma, and eczema. In most of the patients in whom migraine was provoked by non-specific factors, such as blows to the head, exercise, and flashing lights, this provocation no longer occurred while they were on the diet.

Introduction

CHEESE, chocolate, and red wine sometimes provoke migraine, allegedly owing to an idiosyncratic response to a pharmacologically active substance, tyramine.[1] This response is perhaps due to monoamine oxidase deficiency, which has been reported in some patients with migraine,[1] but it is found only during attacks.[2] Double-blind administration of tyramine to patients who benefited from a low-tyramine diet did not provoke attacks of migraine.[3] Deficiency of platelet phenolsulphotransferase in patients with migraine provoked by foods has also been proposed as a possible basis for idiosyncrasy.[4] Food allergies have also been postulated,[5,6] though none has been established by controlled studies. In this study children with severe migraine were given an oligoantigenic diet and in those who improved the causative foods were identified by open reintroduction; responses were confirmed by a double-blind controlled trial of reintroduction of the causative foods.

Patients and Methods

Patients with severe and frequent migraine and their parents were encouraged to participate in a study of dietary treatment, and their informed consent was obtained. Headache due to middle-ear disease, sinusitis, refractive errors, dental disease, raised blood pressure, or intracranial hypertension was excluded. 99 patients were selected who had had headaches at least once a week for the previous 6 months with at least two of the following associated symptoms: pallor, nausea, abdominal pain, photophobia, visual disturbances, giddiness, or weakness and/or paresthesiae down one side of the body. They were investigated and treated as outpatients by one paediatric neurologist (J. E.) and one dietitian (C. M. C.). Existing drug treatment was maintained during the study and patients whose treatment had begun or changed during the previous 3 months were observed for 4 weeks before they entered the study. Throughout the study the patients kept a diary of symptoms and were encouraged to continue full activities.

The oligoantigenic diet consisted typically of one meat (lamb or chicken), one carbohydrate (rice or potato), one fruit (banana or apple), one vegetable (brassica), water, and vitamin supplements (calcium gluconate 3 g/day, 'Abidec' 0·6 ml/day), to suit the tastes of each child, for 3 or 4 weeks, depending on the frequency of headaches. Patients who had no headache or only one during the last 2 weeks of the oligoantigenic diet entered the reintroduction phase. Those who did not improve were offered a second oligoantigenic diet with no foods in common with the first diet. Normal daily helpings of excluded foods were reintroduced singly, one a week. If no reaction occurred, the patient was advised to eat the food regularly. Foods which provoked symptoms were withdrawn at the end of the week. Foods were systematically reintroduced until the diet was nutritionally and socially acceptable. Commercial orange squash (three glasses after appropriate dilution) was given as a source of artificial colour and preservative. If symptoms were provoked, they were investigated further by giving 150 mg tartrazine per day during a second week and 150 mg benzoic acid per day during a third week.

Each patient who responded to foods for which test reagents were available, and who was willing to do so, was asked to enter a double-blind, placebo-controlled, crossover trial which tested the response to one of the foods that had provoked symptoms in the reintroduction phase. The Heinz company kindly prepared tins of individual foods added to a savoury or sweet base; placebo tins contained the bases alone. The savoury base was rice flour, carrots, caramel, sage, onion, and salt, and the sweet base rice flour, banana, sugar, and citric acid. The "active" food tins also contained the following suspected foods (with weights in g of daily intake; content of 2 tins usually equivalent to a normal helping): dried cows' milk (120), dried eggs (60), pork (60), beef (60), chicken (60), wheat (9),

orange juice (44), and haddock (60). These were indistinguishable from the placebo tins in taste, smell, and texture. Patients who had reacted to tartrazine or benzoic acid received capsules containing 150 mg compared with, as placebos, ascorbic acid or calcium lactate. For 6 patients for whom the tins were inappropriate special meals with and without the suspected food were prepared by the dietitian. Patients who had reacted on open provocation to one of these foods but not to the placebo constituents were allocated by random numbers to two groups; one (AP) first received the tins containing the food and then after a "washout" period the placebo; the other group (PA) received the placebo first. Each period lasted 1 week, except in 3 patients with less frequent migraine for whom the period was up to 2 weeks. Trial periods were interrupted in 4 patients who had had at least 3 attacks of migraine or one of complicated migraine. Occurrence of headache and of any migraine-related symptom, preference with respect to any symptom, and identification of active and placebo tins by taste or smell were recorded from the diary and after discussion with one of us (J. E.) before the code was broken. Results were analysed for binary response[7] using the sign test.

Skin-prick tests to twenty-eight antigens (Bencard) were carried out and wheal diameters were measured after 15–20 min. Total IgE and IgE antibodies to sixteen of the same antigens were measured.[8] In the analysis of these results, IgE antibody binding levels twice that obtained with cord serum and total IgE levels >150 IU/ml were taken as critical thresholds. The study was approved by the ethical committee of the Hospital for Sick Children.

Results

Of the 99 patients who entered the study, 11 later withdrew. 88 completed the oligoantigenic diet: 6 did not improve at all, 78 recovered completely on the first or second oligoantigenic diet, and 4 improved greatly. Of the 82 who improved, all but 8 relapsed on reintroduction of one or more foods. These 8 have remained well. The 74 who relapsed were considered for the controlled trial but 28 were excluded for various reasons (no appropriate tin, reacted to placebo tin, unwilling, or ready after trial was complete), and 2 patients left the trial after accidentally breaking the diet and 4 after refusing the tins. The trial was closed when 40 patients had completed it.

The 88 patients (40 boys, 48 girls; age 3–16 years, mean 9·83 years) had had migraine for 6 months–11 years (mean 3·75 years). 39 had migraine with typical prodromal symptoms and 49 common migraine. 48 had a history of atopic disease. 65 had a first-degree relative with migraine and 64 one with atopic disease. Associated symptoms are shown in table I. Some patients had no further symptoms after the start; others took over 3 weeks to recover. In some children some symptoms became worse at first, especially lassitude, headaches, and irritability, and sweating and tremor occasionally occurred. The 6 patients who did not respond had common migraine; 3 had positive skin-prick tests. 6 patients had persistent neurological signs ascribed to cerebral infarction and all 4 who had computed tomography of the brain had abnormal scans.

Almost all patients had behaviour disturbance at the time of an attack, but 41 also had behaviour disturbance (mostly hyperkinetic) at other times. In those whose headaches responded on the oligoantigenic diet most of the associated symptoms (table I), except the permanent neurological abnormalities, also responded. Antiepileptic drugs were withdrawn in those who became fit-free, without recurrence of fits unless the diet was broken. Many of these symptoms recurred on reintroduction of foods. In 18 patients open provocation on 27 occasions with several foods caused behaviour disorder without headache, whereas other foods caused migraine. This pattern was reproducible in patients given the foods repeatedly.

TABLE I—ASSOCIATED SYMPTOMS AND SIGNS

—	Patients completing oligoantigenic diet (88)		Patients completing trial (40)	
	Before diet	On diet	Group AP	Group PA
Abdominal pain, diarrhoea, flatulence	61	8	14	19
Behaviour disorder	41	5	12	16
Aches in limbs	41	7	12	17
Fits	14*	2	5	5
Permanent neurological signs	6	6	1	4
Rhinitis	34	15	5	9
Recurrent mouth ulcers	15	2	4	6
Vaginal discharge	11	1	3	5
Asthma	7	3	1	1
Eczema	6	3	3	4

*Sometimes coinciding with headaches in all 14: 9 had generalised or partial seizures, coinciding with headaches in all but 1.

Of the 40 patients who completed the trial, 17 were allocated to group AP and 23 to group PA. The mean age and the prevalence of the various symptoms of migraine did not differ between the two groups (table I). 5 mothers thought they could distinguish the active and placebo tins by taste or smell but only 2 were correct. There was no significant order effect in the occurrence of headaches or any migraine-associated symptom or in the preference for either type of tins, but there were highly significant relations between the active material and symptoms for all three assessments (table II).

Excluded foods were reintroduced according to the taste and views of the child and family, so not every child had every food. 8 children had no symptoms when any food was given, and 17 had symptoms with only one, but most children reacted to several foods (up to twenty-four), from which one was selected for testing in the trial. The child who reacted to twenty-four foods was symptom-free on a nutritionally adequate and acceptable diet avoiding all these. Patients were

TABLE II—OCCURRENCE OF HEADACHE, OR OF ANY MIGRAINE-RELATED SYMPTOM, AND PREFERENCE FOR ACTIVE OR PLACEBO TINS

—	Headaches			Migraine-associated symptoms			Preference		
	AP	PA	Total	AP	PA	Total	AP	PA	Total
Neither food	2	6	8	1	2	3	1	2	3
Active food	14	12	26*	12	15	27*	0	2	2*
Placebo	0	2	2*	0	2	2*	16	19	35*
Both foods	1	3	4	4	4	8	..	..	
Total	17	23	40	17	23	40	17	23	40

*Difference between active and placebo; $p<0·001$.

TABLE III—NUMBER OF CHILDREN IN WHOM FOODS CAUSED SYMPTOMS

Food	n	Food	n	Food	n	Food	n
Cows' milk	27	Soya	7	White wheat flour	3	Vegetable oils	2
Egg	24	Tea	7	Artificial milk		Lentils	2
Chocolate	22	Oats	6	substitute	3	Peas	2
Orange	21	Goats' milk	6	Banana	3	Ice cream	2
Wheat	21	Coffee	6	Strawberries	3	Rabbit	1
Benzoic acid	14	Peanuts	5	Melon	3	Dates	1
Cheese	13	Bacon	4	Carrots	3	Avocado	1
Tomato	13	Potato	4	Lamb	2	Rhubarb	1
Tartrazine	12	Yeast	4	Rice	2	Leek	1
Rye	12	Mixed nuts	4	Malt	2	Lettuce	1
Fish	9	Apple	4	Sugar	2	Cucumber	1
Pork	9	Peaches	4	Ginger	2	Cauliflower	1
Beef	8	Grapes	4	Honey	2	Mushrooms	1
Maize	8	Chicken	3	Pineapple	2	Runner beans	1

usually very fond of the provoking foods, sometimes craving them, and often ate very large amounts. Cows' milk caused symptoms in most children. All but 1 of those reacting to milk also reacted to cheese, whereas 13 reacted to cheese but not to cows' milk. Sheep-milk and goats'-milk cheese, given to those who had reacted to cows' milk cheese, caused no symptoms. Fifty-five foods provoked symptoms (table III). No other obvious repeated combinations of foods were noted. In some children symptoms were provoked by tartrazine or chocolate and by other foods with no obvious chemical (idiosyncratic) similarities, such as egg or wheat. Processing a food may affect its tendency to provoke symptoms; some patients reacted to white wheat flour but not to brown, and 4 reacted to bacon but not to pork. Those who reacted to peanuts (a legume) were separate from those who reacted to other nuts, and 1 of the 2 who reacted to sugar reacted to cane sugar but not to beet sugar. The median reaction time for recurrence of symptoms was 2 days (range <1 h–>7 days). Symptoms disappeared again usually in 2–3 days (range <1–21 days). 14 families had suspected provoking foods and 11 of these were confirmed; however, all but 1 patient also had headaches with other unsuspected foods. Abdominal pain and distension was usually the first symptom and was the only symptom after 48 different food challenges.

38 of the patients successfully treated by diet reported non-dietary provocation before treatment (table IV). During the diet period smoke and perfume still provoked migraine, but only 3 patients still had symptoms after exposure to the other factors.

45 patients (52%) had positive skin-prick tests to one or more of the five antigens we use routinely for identifying atopic subjects (timothy grass pollen, *Dermatophagoides pteronyssinus*, cat fur, cows' milk, and hens' eggs). 63 patients (72%) gave positive reactions to one or more of twenty-eight antigens tested. No difference in response to diet was noted between patients with or without positive prick tests to one or more of the five or the twenty-eight antigens. Though some prick tests for foods which caused symptoms were positive (table V) the association was not strong and only 3 patients would have recovered if they had avoided only the foods to which they had positive prick tests. Similarly 28% of the 64 patients tested had high serum IgE levels, but IgE antibodies were not helpful in identifying causative foods (table V).

TABLE IV—NON-SPECIFIC PROVOKERS OF MIGRAINE IN 38 PATIENTS

—	Before diet	On diet
Exercise	13	1
Trauma	11	1
Emotional	10	0
Perfumes and/or cigarette smoke	10	9
Travel	9	0
Bright light	5	0
Heat	2	1
Noise	2	0

2 patients, though they recovered on the oligoantigenic diet, decided to return to a full diet and drug treatment. The rest have all remained on their diets, without any evidence of adverse effects, symptom-free except after occasional breaks of diet, off antimigraine drugs, and usually off antiepileptic drugs. 5 patients have used sodium cromoglycate (400 mg before the meal) before planned breaks of the diet and have remained free of symptoms. After more than a year of successful diet 5 patients noted that they no longer got symptoms when they took some or all of the causative foods and have expanded the diet, 2 without restriction or relapse.

Discussion

This trial shows that most children with severe frequent migraine recover on an appropriate diet, and that so many foods can provoke attacks that any food or combination of foods may be the cause. Intolerance to such a wide range of foods suggests allergic disease rather than metabolic idiosyncracy. The high prevalence of other atopic disease in the children and their first-degree relatives and the high frequency of positive skin-prick tests support this view, but there was no great excess of raised IgE or IgE antibodies.

Migraine is strongly influenced by emotional factors, as are most allergic diseases. Drug trials have shown large placebo effects.[9] We (except J. F. S.) embarked on this study believing that any favourable response, such as that claimed to substantiate the dietary hypothesis,[1,5,6] could be explained as

TABLE V—ASSOCIATION OF POSITIVE SKIN-PRICK TESTS AND IgE ANTIBODIES TO FOODS WITH PROVOCATION OF CHILDHOOD MIGRAINE

—	Skin-prick* test	IgE antibodies†
Number of tests positive for a provoking food	57	8
Number of tests negative for a provoking food	141	152
Number of tests positive for a non-provoking food	80	24
Patients who would be cured by avoidance of indicated foods	3	0

*Twenty-one food antigens tested in 87 patients. Wheal diameter >3 mm taken as positive.
†Fifteen food antigens tested in 76 patients. Binding >2× cord serum taken as positive.

a placebo response. The positive double-blind controlled trial with little order effect and the fact that different combinations of a few foods reproducibly provoked symptoms in each child provide clear evidence that a placebo response was not the explanation.

Single foods or combinations may evoke rapid or slow responses in food-allergic diseases.[10] Slow responses often require large amounts of several foods and are difficult to diagnose; food-allergy migraine is probably one of these. Only a study with a considerable amount of a food for several days would detect slow responses. Though we could include in the trial only half the patients seen, the exclusions are unlikely to have been selective, so our findings are probably applicable to the rest of our patients, 93% of whom responded to diet. However, we cannot securely extrapolate to other groups of patients, such as those with infrequent mild migraine or adults. With this trial as a basis, less rigorous protocols, preferably with double-blind provocations to confirm the effect, will be needed to establish the full potential of diet treatment in those patients ill enough to justify it. Diets are dangerous[11] and socially disruptive, so such treatment should be adopted only when the symptoms are severe and only under experienced medical and dietetic supervision. In uncontrolled attempts to extend the application of diet treatment, we studied 3 patients with alternating hemiplegic migraine, excluded from the trial by protocol; they failed to respond to 3 weeks of oligoantigenic diet. However, impressed by their children's favourable responses, 7 parents have also been successfully treated by diet.

The failure of non-specific factors to provoke migraine when our patients were on appropriate diets suggested that the responses to such factors may result from a chronic alteration of the non-specific responsiveness of the appropriate vascular end-organ as a result of long-term antigen contact. This mechanism would be analogous to the response of the bronchioles to exercise or cold after antigen contact in asthma. The persistence of a response to smoke and perfume suggests that inhaled antigens may also provoke migraine.

The observations that 8 patients who responded to the diet did not relapse on reintroduction of foods and 2 who responded to a food in the trial ceased to do so after a period on maintenance diet could be due to spontaneous recovery of allergy while on the diet (a phenomenon recognised in other food allergies such as eczema), to a change of the family diet resulting from general dietary advice, or to a placebo effect.

If a patient avoids only some of the foods that provoke symptoms, he may eat more of other provoking foods and so have worse symptoms. If only foods high in tyramine, such as cheese and chocolate, had been avoided in our study, only 5 patients would have recovered, so a controlled trial of such a valid treatment would have been negative. The same would be true of avoidance of food colours and preservatives, although they appear to be important causes of migraine. This phenomenon may explain the essentially negative controlled trials of such diets in patients with behaviour disorder.[12] Oligoantigenic diet trials are needed in such patients too.

The lack of IgE antibodies to many of the causative foods, the slow response, and the lack of obvious differences between atopics and non-atopics suggest that IgE may not be important in the mechanism of the presumed allergy. When provoking foods were given, abdominal symptoms usually recurred first; the allergic reaction may therefore occur in the gut, and the other manifestations may result from released mediators or from circulating antigen or antigen-antibody complexes. However, patients with and without gastrointestinal symptoms responded equally well. Diets influence intestinal flora, but this is unlikely to be the mechanism for response to individual foods. We cannot equate our findings with reports of deficiencies of monoamine oxidase[2] or phenolsulphotransferase[4] in some patients with migraine. However, abnormalities of platelet function[13] are as compatible with an allergic as with an idiosyncratic hypothesis.

It is encouraging that the transient symptoms of migraine patients with permanent hemiplegia and computed tomographic evidence of infarcts respond to diet as well as do those without such chronic damage. Symptoms other than headache which responded to diet in our patients included both those known or suspected to be caused by food allergy and others (eg, epilepsy, limb pains) not usually associated with food allergy. In the patients who stopped having fits anticonvulsant drugs were withdrawn without recurrence of fits while they remained on the diet. Patients with migraine and epilepsy and probably many with epileptic headache are likely to benefit from the diet. Since many of these symptoms occurred after foods other than those causing headaches, the possibility of food allergy as a cause of these symptoms in children without migraine needs further study. Identification of food allergy is important since it is easily treatable and the benefit our patients experienced was often very great.

It is unfortunate that no tests are available for identifying the causative foods, since the oligoantigenic diet is very demanding. However, this is the first series of patients with a presumed slow food allergy in whom the response of each patient to each food is established, and who have had a wide range of potential diagnostic tests. Further analysis of these data are required before the usefulness of these tests is rejected, and there are many possible tests to assess. We have not done intradermal tests because they are painful and potentially dangerous.

We have yet to assess empirical diets such as that which we established for eczema.[14] Claims of benefit in food allergy from oral or parenteral hyposensitisation or rotation diets have not been substantiated by controlled trials; thus, there is no alternative to the oligoantigenic diet at present. Even when the appropriate diet is established, continued skilled care and supervision are needed. Recovery may occur. We have some uncontrolled data that, as in eczema[15] the diet may occasionally be broken briefly without symptoms if the patient takes oral sodium cromoglycate first; we think that, as with eczema, the drug is only an ancillary to effective diet, but such use can be of great social benefit.

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References at foot of next column

EXPERIMENTAL TRANSMISSION OF SIMIAN ACQUIRED IMMUNODEFICIENCY SYNDROME (SAIDS) AND KAPOSI-LIKE SKIN LESIONS

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Summary A disease that is similar to human AIDS may occur in monkeys. Simian AIDS (SAIDS) was experimentally transmitted from 2 rhesus monkeys dying of the disease to 4 cytomegalovirus (CMV) antibody-negative rhesus monkeys. The inocula consisted of the supernatant fluid from 10% homogenates of various tissues with or without buffy-coat cells from blood. Lymphadenopathy, splenomegaly, neutropenia, polymyositis, and other signs of the disease appeared in recipients within a few weeks after inoculation. Two animals developed Kaposi-like "patch" and "plaque" skin lesions and one died of sepsis and profound lymphoid depletion. A second animal also died with lymphoid depletion. All animals became infected with CMV but antibody levels were low in two animals, appeared and then disappeared in one, and never developed in the second monkey which died.

Introduction

ACQUIRED immunodeficiency syndrome (AIDS) is a highly fatal disease, characterised by cellular immune deficiency, hypergammaglobulinaemia, opportunistic infections, and/or malignancies. Patients at high risk include homosexual and bisexual men, intravenous drug users, Haitians, female sexual partners of AIDS patients, haemophiliacs and others who are given blood or blood products, and children living in households with AIDS patients or born to mothers with AIDS.[2,3] The cause of the disease is unknown, but epidemiological data suggest that AIDS is caused by an infectious agent, most likely a virus. Failure to transmit AIDS to animals has hampered progress in the understanding of its aetiology and pathogenesis.

We recently described a spontaneous outbreak of a simian AIDS-like disease (SAIDS) in 64 rhesus monkeys (*Macaca mulatta*) housed outdoors at the California Primate Research Center at the University of California, Davis, California.[4] The disease in monkeys, like that in man, is characterised by generalised lymphadenopathy, severe opportunistic infections, chronic wasting, and high mortality. Several animals had subcutaneous fibrosarcomas. A somewhat similar disease has also been reported from the New England Regional Primate Research Center in Southborough, Massachusetts.[5]

In this paper we describe the successful transmission of SAIDS to rhesus monkeys inoculated with tissues from two animals which died of the natural disease.

Materials and Methods

Animal Inoculation

Two rhesus monkeys in the advanced stages of SAIDS and judged to be near death were killed in November, 1982, and January, 1983. These animals were members of a group housed in the outdoor corral at the California Primate Research Center, which was having an epizootic of SAIDS.[4] Blood was withdrawn from each animal before they were killed and tissues removed at necropsy were placed on wet ice and flown the same day to the National Institutes of Health (NIH), Bethesda, Maryland, for examination. On arrival at NIH, homogenates of tissues were prepared and used as inocula in transmission experiments.

Inocula consisted primarily of the supernatant fluid from 10% homogenates of various tissues. Tissues were aseptically homogenised for 30 s in Eagle's minimum essential medium without antibiotics. The suspensions were clarified by low speed centrifugation (200 *g*, 10 min). All recipient monkeys were females 10–15 months of age and had no detectable rhesus cytomegalovirus antibody.

SAIDS-1 Inoculum

The donor monkey for the first study (SAIDS-1) was a 2½-year-old female with splenomegaly, chronic gastroenterocolitis, fibrinopurulent interstitial pneumonia, and generalised lymphadenopathy. Lymph-nodes showed cortical and paracortical lymphoid depletion and sinus histiocytosis with marked erythrophagocytosis. Plasma cells were absent. The axial skeletal muscle showed lymphohistiocytic myositis, fasciitis, and lymphocytic synovitis. Cytomegalic cells were present in the liver, spleen, and several lymph nodes. *Cryptosporidium sp* was found in the gall bladder, small intestine, and colon. *Staphylococcus aureus* was isolated from the lung and *Campylobacter fetus* subsp *jejuni* was isolated from the gut.

Two rhesus monkeys, no 1 (B-784) and no 2 (B-649), were each inoculated intravenously with 3·25 ml of supernatant fluid from an unfiltered 10% homogenate of bone marrow, lymph node, spleen, and salivary gland to which was added 0·25 ml of buffy coat cells obtained from 5 ml of heparinised blood. Thus, the total volume of inoculum per animal was 3·5 ml.

SAIDS-2 Inoculum

The donor monkey for the second study (SAIDS-2) was a 3½-year-old female with a subcutaneous fibrosarcoma in the mandibular region. Lymph-nodes showed cortical and paracortical lymphocyte

J. EGGER AND OTHERS: REFERENCES

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