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A Role for Food Intolerance in Childhood Migraine

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Abstract

Provocation of migraine by dietary components has been clearly described in the medical literature for over 100 years. Competing immunologic and metabolic concepts of pathogenesis have been proposed. The metabolic concept inroducted by Alex Russell[1,2,3] was based upon inherited enzyme deficiencies, in some apparently increasing the sensitivity of migraineurs to vasoactive substances consumed in food. Deficient activity of monoamine- and diamine-oxidases and of phenolsulphotransferase have been described. Phenolic amines have been suggested as triggers. The failure of tyramine administered alone to provoke migraine in children has dampened enthusiasm for this hypothesis, although Russell's concept of a specifically metabolic and X-linked genetically determined form of hyperammonemic migraine has not been refuted. The immunologic concept assumes a delayed allergic mechanism. Egger proposed a two-stage process in migraine provocation: allergic reaction to foods increases intestinal permeability to vasoactive substances derived from food or gut flora.

Marteletti and his colleagues have found evidence of altered immune activation in pediatric and adult migraine. Following food challenge their subjects demonstrate an increase in circulating immune complexes and in total and activated T-cells.

Egger et al have published the only double-flind placebo-controlled trials of food intolerance in childhood migraine, confirming specific food sensitivities in 52% of children with severe, frequent migraine. An average delay of two days between exposure and symptom supports the thesis that provocation occurs in stages. Egger, McEwen and Stolla subsequently demonstrated that children with food-induced migraine could be desensitized to their food triggers by an immunologic hyposensitization procedure. At the study'' end, 80% of children receiving active treatment and 25% of children receiving placebo were able to resume a full normal diet without experiencing migraine attacks ($p=0.001$).

These studies support a role of immunologic hypersensitivity in the genesis of migraine in food-intolerant children.

INTRODUCTION

Migraine headache and food intolerance are ancient phenomena, each

mentioned in the Hippocratic texts. Pediatric migraine as a distinct disorder received relatively little attention until the middle of this century when Vahlquist established strict criteria for its definition. These were paroxysmal headache separated by pain-free intervals, associated with two fo the following four features; nausea or vomiting, visual aura, positive family history of migraine, unilateral distribution of throbbing pain.[4] In studies conducted twenty years apart in different countries, Bille[5] and Silanpaa[6] found the prevalence of migraine among schoolchildren to be approximately 4%, using Valquist's criteria.

A role for dietary components in provoking attacks of migraine was first clearly described in Living's classic monograph of 1873, which included four cases of food-induced migraine[7]. During the first half of this century, numerous reports of an association between migraine and food appeared, most attributing headache to allergy[8-13]. The weak association between food-induced migraine and total IgE levels or the results of cutaneous prick tests, however, led some authors to doubt the existence of allergic headache[14-17].

BIOCHEMICAL PROVOCATION OF MIGRAINE

Over the past three decades, competition between immunologic and pharmacologic mechanisms for food-induced migraine has received considerable attention. The pharmacologic concept was initiated by Hannington in 1967, when she proposed that food-borne tyramine, not anti- genic protein, was the trigger[18]. In subsequent reports, Hannington and her colleagues suggested that migraineurs are sensitive to tyramine because of a deficiency of monoamine oxidase in plateletsl[19,20]. The defect in monoamine oxidase proved to be transitory, however, a result rather than a cause of the migraine state[21], and the group's attention turned to a persisting deficiency of platelet phenolsulphotransferase as the underlying biochemical defect in migraine[22]. Phenolsulphatransferase not only inactivates phenylethylamines[23] but also metabolizes other foodderived phenols such as the flavonoids which may act as triggers for red wine headache[24]. Additional candidates for the chief biochemical trigger of migraine have been advanced by researchers in Sweden, Canada and Germany, based upon response to exclusion diets. These include tryptophan, the precursor of serotonin[25], phenylalanine, the precursor of norepinephrine (which stimulates platelet serotonin release)[26] and histamine (which allegedly accumulates because of a deficiency of diamine oxidase)[27]. The notion that food chemicals provoke migraine because of enzymatic deficiency implies an inborn error of metabolism, yet very few children with migraine have been studied biochemically. During two double-blind placebo-controlled trials of tyramine feeding, Forsyth and Redmond were unable to induce migraine headache in children[28]. A similar study in adults also yielded negative results[29]. It seams unlikely that monoamines alone are the principal. food triggers for pediatric migraine, although Russell's concept of a specifically metabolic and X-linked genetically determined form of hyperamnionemic migraine has not been refuted. Indeed, the vindication of its X-linked transmission supports its analogy as one form of classical migraine[1].

IMMUNOLOGIC EVENTS IN THE GENESIS OF MIGRAINE

Marteletti and his colleagues have found evidence of immunologic disturbance following food challenges in patients with ostensibly food-related migraine, specifically an increase in circulating immune complexes and activated T-cells[30,31] and a decline in circulating levels of IL-4 and IL-6 accompanied by an increase in gamma-IFN and GM-CSF[32].

They have also demonstrated protection against precipitation of migraine attacks by oral administration of sodium cromoglycate, a stabilizer of mast cell membranes[33]. Prophylactic benefits of sodium cromoglycate in adult migraine have been demonstrated by Mansfield et al in a double-blind placebo-controlled trial[34] and by Monro et al[35,36]. Paganelli found that ingestion of allergenic foods by atopic individuals produces an increase in circulating immune complexes containing food protein, which can be attenuated by pretreatment with cromolyn sodium[37]. Doering has proposed that failure of migraineurs to clear food-containing circulating immune complexes may precipitate an immunologically mediated headache and that susceptibility to immunecomplex phenomena cannot be detected by prick tests or IgE measurements[38].

Egger has attempted to weld together immunologic and pharmacologic mechanisms in migraine with his proposal that food allergic reactions cause an increase in small intestinal mucosal permeability which allows excessive absorption of vasoactive substances from the gut, derived either from food or from the endogenous flora[39]. His theory receives indirect support from the work of Andre and of Dupont in Paris. Each has demonstrated that ingestion of food allergens by atopic children causes an increase in para-cellular permeability of the small intestine to biochemical substances such as the disaccharide lactulose, which are ordinarily not absorbed from the intestinal tract. Dupont found a weak correlation between prick test results and increased permeability in response to food challenge, but a strong clinical correlation between provocation of allergic symptoms and an increase in permeability on challenge[40,41]. Andre was able to show that pre-treatment with cromolyn attenuated the permeability increase[42] and concluded that the increase in permeability in response to food is more sensitive and specific than prick tests or RAST and by itself constitutes an accurate diagnostic test of food allergy[43]. If food-induced eczema is considered a model for immunologic food allergy, then the inconsistent relationship between prick test or RAST results and clinical response to food challenge is found in atopic eczema as well as migraine and does not constitute evidence against an immunologic basis for migraine. In contrast the protective effect of sodium cromoglycate in both conditions suggests a pathogenetic role for gut mast cells.

OLIGOANTIGENIC DIETS FOR MIGRAINE

In 1970, McEwen and Constantinopoulos published the results of a prospective trial of diet in so-called "intrinsic" asthma[44]. Three years later, Professor Soothill of the Hospital for Sick Children, Great Ormond Street, London, began investigating the role of non-atopic dietary hypersensitivity in a number of common diseases of childhood, including migraine. Soothill accepted six principles for dietary trials of nonatopic food sensitivity which had been set down by McEwen. These are:

(1) The essential baseline for further investigation is a symptom-free patient on a formal diagnostic diet.

(2) Because food intolerances are often multiple, the diagnostic diet must be limited to a small number of foods which are unlikely to provoke intolerance (oligoantigenic).

(3) Because non-atopic sensitivity often provokes prolonged and fluctuating symptoms, the diagnostic diet must be administered for sufficient time to allow remission to occur and b_~ clearly recognized, usually two to three weeks.

(4) Because the symptoms of food intolerance are often delayed, testing by dietary reintroduction of foods which have been avoided must be

restricted to one new food per week, which is eaten daily during the challenge period.

(5) As the dose-response curve of food intolerance is bell-shaped, challenge with Virget foods should be done using normal quantities, not excessive quantities.

(6) Because valid dietary testing requires that a food substance be absorbed through the usual pathway at the usual rate, each food must be tested in the form in which it is normally consumed.

Based on these principles, Egger, Carter and Soothill developed a standard diagnostic protocol and used it for two trials. In the first they studied childhood migraine 45, in the second hyperkinetic syndrome/attention deficit disorder[46]. All stages of the work were carried out while the children lived at home. The response of children to the diagnostic diet and reintroduction of foods were first determined by open experiment. The initial oligoantigenic diet was followed for four weeks. It consisted of one meat (chicken, lamb or turkey), one starch (potatoes or rice), one fruit (apples, pears or bananas), one vegetable from the brassica family, sunflower oil, a multivitamin, calcium and mineral water. The results were assessed by parents at home and by doctors during visits to the clinic. At the conclusion of the open phase of the trials, each child was considered to be food-intolerant if he remained symptom-free on the oligoantigenic diet and relapsed with addition of specific foods. To be included in the second phase, each child had to remain symptom-free by avoiding only those foods to which he was thought to be reactive. In phase two, the results of the open trial were tested in a double-blind, placebo-controlled cross-over experiment. One food to which the child had reacted in the open trial was consumed daily for a week, in a disguised form, indistinguishable from placebo, in quantities which the child would normally eat. The base in which the foods were hidden consisted of rice flour, carrot or banana, caramel, onion and salt or cane sugar and citric acid. Accuracy of blinding was assessed by the investigators. Only 5% of parents were able to correctly separate placebo and active challenge food by taste or smell. Most parents were unable to distinguish one substance from another and 12% guessed incorrectly.

The migraine study involved 40 boys and 48 girls, aged 3 to16, with headaches occurring at least once a week for six months to eleven years (mean 3.73 years), associated with two of the following symptoms: pallor, photophobia, dizziness, nausea, abdominal pain, visual disturbances or focal neurologic deficits. Classical migraine was the diagnosis in 39, common migraine in 49. During the open trial, 78 children (89%) became symptom-free and 4 children greatly improved. Relapse with refeeding of specific foods occurred in 90% of the

Table 1
Foods provoking migraine
in 76 children
(Egger et al, Lancet 1983)

Foods Tested	*% Provoked*
Cow's milk	39
Chocolate	37
Benzoic acid	37
Hen's eggs	36
Tartrazine	33
Wheat	31
Cheese	31
Citrus	30
Coffee	24
Fish	22
Corn	17
Grapes	17
Goat's milk	16
Tea	16
Pork	13
Beef	12
Beans	12
Malt	9
Lentils	9
Apples	8
Yeast	7
Pears	6
Apricots	6
Cane sugar	5
Potatoes	5
Peas	5
Banana	5
Carrots	4
Chicken	4
Peaches	4
Lamb	3
Rice	1

Brassicas	1

responders. The interval between exposure and provocation varied from one hour to one week but averaged two to three days. The number of foods which provoked headache ranged from one to twenty-four. The frequency with which specific foods provoked headache is shown in Table 1. Forty children were selected for the double-blind placebo-controlled crossover study, the results of which are summarized in Table 2. This trial confirmed 65% of the food reactions identified in the open trial, using the strictest criteria available for clinical studies. Considering the total group of 88 children with severe and frequent migraine, 52% were shown to be intolerant of specific foods in this experiment. It is of note that when children were maintained on a dietary regime devoid of provoking foods, they were also resistant to other, non-specific triggers which had previously been thought to activate migraines, such as emotional distress, physical activity and temperature change.

When the trial of children with attention deficit disorder produced similarly dramatic results, the findings were challenged by Professor P. J. Graham in the Department of Psychiatry at Great Ormond Street and Dr. Eric Taylor, Head of Child Psychology at the Maudsley Hospital. A second study involving hyperkinetic children was instituted at Great Ormond Street, with the sceptical participation of Graham and Taylor, and the results of the first study were confirmed[47].

Table 2. Results of double-blind placebo-controlled cross-over trial, 40 children, one food each
(Egger et al, Lancet 1983)

Trigger	A-P	P-A	Total
Neither food	2	6	8
Active food	14	12	26*
Placebo food	0	2	2*
Both foods	1	3	4

Soothill's group also studied 36 children with refractory epilepsy, half of whom suffered from migraine and half of whom did not. None of the children Nvith epilepsy alone responded to diet but 89% of the children with both epilepsy and migraine showed improvement in both sezures and headaches during the oligoantigenic diet[48]. The strong association between reactions to cow's milk and cow's cheese but not sheep cheese was interpreted by the authors as indicating an allergic mechanism rather than a biochemical mechanism.

Four other studies performed in children have since found a positive effect of oligoantigenic diets in migraine, although none attempted to confirm their findings with a double-blind placebo-controlled followup[49-52]. In all studies, long term improvement in frequency mid severity of headache was achieved by those children who complied with the specific food elimination diet., but compliance was often difficult. In some cases, re-exposure after prolonged avoidance (e.g. two years) was no longer associated with provocation of symptoms, indicating a loss of sensitivity.

HYPOSENSITIZATION FOR FOOD-INDUCED MIGRAINE

In 1992. Egger, McEwen an J. Stolla completed a double-blind placebo-controlled trial of immunologic hyposensitization for children with food-induced migraine at Universitatskinderklinik, Munich (unpublished results). Children with frequent severe migraine were initially selected by the methods used in the study of diet and pediatric migraine at Great Ormond Street, ie freedom from headache during the oligoantigenic diet period and provocation of headache upon exposure to individual foods. Participation in the hyposensitization trial was offered to children who fulfilled these criteria but for whom a safe diet was unacceptably restricted. The active treatment consisted

of an intradermal injection of food antigens mixed with the enzyme beta-glucuronidase, a technique developed by McEwen called Enzyme-Potentiated Desensitization (EPD)[53]. A parallel. study of EPD in food-sensitive hyperkinetic children was conducted at the same time; the protocols were the same in both trials[54].

Forty children took part in the double-blind placebo-controlled trial of hyposensitization for migraine, each receiving an injection of placebo or active material every eight to ten weeks for a total of three injections. Provoking foods were

avoided during the treatment period. Three weeks after the third injection, foods shown to provoke symptoms during the open trial were again reintroduced. The outcome was assessed by a single criterion: the ability of each child to resume a full normal diet without recurrence of migraine. The results of this experiment, which involved forty children, are shown in Table 3. Eighty per cent of children receiving active treatment, but only twenty-five per cent of those receiving placebo, were able to resume a normal diet without recurrence of headache (p=0.001).

Table 3
Enzyme-potentiated densensitization for childhood migraine, response to double-blind, placebo-controlled trial

	EPD	Placebo
Food tolerant	16	5
Still reactive	2	10
Inconclusive	0	1
Dropped out	2	4

The adjuvant role of beta-glucuronidase in enhancing hyposensitization was discovered by McEwen in 1967[55]. Uncontrolled case reports of the usefulness of EPD for hyposensitization of adolescents and adults with immediate hypersensitivity responses to specific foods were first published in 1975[56]. Double blind placebo-controlled trials have demonstrated the effectiveness of EPD in decreasing the symptoms of seasonal allergic rhinitis provoked by grass pollen[56] and in hyposensitization of children with food-induced hyperkinetic syndrome[54]. The mechanism by which EPD reverses food intolerance is not known. Its effectiveness in the treatment of hayfever[57] implies an immunologic effect. Nonetheless, unlike conventional pollen desensitization, which elicits production of blocking antibodies[58], EPD treatment of patients with allergic rhinitis does not induce blocking antibody (MS Starr, personal communication). Antigen-induced

leukocyte migration inhibition demonstrates in vitro a cell-mediated immune response which is present in IgE-mediated hayfever[59]. The leukocytes of cow's milk-sensitive patients with atopic eczema are also inhibited by cow's milk in this test. Brostoff showed that after successful EPD for milk allergy this inhibition disappeared (J. Brostoff, personal communication). This finding suggests that EPD hyposensitizes by reducing cellular responsiveness to allergens. The effectiveness of EPD in the treatment of childhood migraine gives weight to the hypothesis that

the basis of migraine *for most children* is a non-atopic immunologic response to foods or other antigens.

A parallel to the combined immunologic/metabolic hypersensitivity of migraineurs can be found in atopic asthma. It is now widely accepted that atopic asthma has multiple mechanisms of pathogenesis. Contact with specific allergen (e.g. house dust mite) triggers immunologic hypersensitivity[60,61], but hyper-responsiveness of the airway to pharmacologic mediators (e.g. histamine[62]) is also extremely important. Prolonged allergen avoidance not only decreases the frequency of allergen triggered asthmatic attacks but also decreases non-specific bronchial reactivity to histamine challenge[63]. Asthma is thus an excellent model of the immunologic priming of pharmacologic responsiveness. We believe that lessons learned from asthma research are relevant to migraine and that, for migraine, altered intestinal permeability may be a link between humoral/metabolic and immunologic reactivity.

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