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IgG-mediated allergy: A new mechanism for migraine attacks?

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Despite recent advances offered by modern neuroimaging and genetic techniques, the pathophysiology of migraine has not been fully clarified. As pointed out by Selby and Lance 50 years ago, a relevant proportion of patients report that their migraine attacks are usually precipitated by dietary items (1). In a survey analysing the prevalence of dietary migraine in 500 new migraine patients, Peatfield et al. found in 1984 that 19.2% of migraine patients reported sensitivity to cheese, 18.2% to chocolate ad 11.1% to citrus fruit (2). The same year, Monro et al. published a paper in the *Lancet* with the categorical title 'Migraine Is a Food-Allergic Disease', describing the treatment of just nine patients with severe refractory migraine with either sodium cromoglycate or placebo after the patients ate foods previously identified as provocants (3). Sodium cromoglycate exerted a protective effect, which made the authors conclude that a food-allergy reaction is the cause of migraine, at least in this group of patients with dietary precipitants. Definite proof that this is a reproducible fact, however, has proved elusive. In other studies objective evidence of hypersensitivity was found in very few cases, and those reporting a reduction in migraine during formal diets not only include a low number of patients, but mostly make no serious attempt to conceal the dietary strategy from the patients, pay insufficient attention to placebo effect and include an incredible prevalence of atopic diseases in migraine patients.

One of the obstacles to acceptance of the dietary hypothesis is the lack of a clear scientific explanation of the mechanisms implicated in the development of migraine attacks supposedly precipitated by food. The first obvious proposed mechanism was an allergy mediated by IgE antibodies. Theoretically, the interaction of a food constituent with a specific IgE antibody would produce a response by activation of complement or degranulation of mast cells. Several independent studies have failed to find elevated IgE levels or complement activation during migraine attacks, even in patients with a history of food-precipitated headaches (4,5).

These results, together with the finding that diet-sensitive patients are usually sensitive to several and different foods, led to the next proposal for a common pathogenic mechanism: antigenic similarities between these disparate foods seemed less likely than sharing a common chemical constituent (2). Investigators tried to confirm the so-called 'amine hypothesis' first by clinical challenge tests with substances like tyramine or β-phenylethylamine. As elegantly reviewed by Peatfield (5), the results of these studies can be interpreted as inconsistent. The next step was to investigate the amines' metabolic routes. Could the elimination pathways of such amines be deficient in dietary migraine patients? There are two major breakdown pathways for these substances in humans: oxidation by monoamine oxidase (MAO) to parahydroxyphenylacetic acid and sulphation by phenosulphotransferase to water-soluble conjugates. MAO, a mitochondrial enzyme, exists in two forms in humans, with different substrate specificities. MAO A predominates in gut mucosa and liver and preferentially inactivates catecholamines and serotonin. The human platelet contains only MAO B, which metabolises phenylethylamine, benzylamine and methylhistamine. Tyramine and dopamine are substrates for both forms (6). The easy availability of platelets led to MAO B being the only form to be studied in migraine patients. Most studies have found a low platelet MAO B activity but only during migraine attacks, both in dietary and non-dietary patients (5). The significance of these findings remains uncertain. The sulphation route has also been explored in migraine patients. A reduced urinary output of sulphated tyramine metabolites after an oral tyramine load in subjects with food-sensitive migraine

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has been reported. Phenolsulphotransferase, the enzyme responsible for sulphate conjugation, has been found to exist in two forms: the phenosulphotransferase M, which sulphates the amines, including tyramine, dopamine and catecholamines, and the phenosulphotransferase P, for which no endogenous substrate has been identified (7). In studies of these two enzymes in migraine patients, only in the case of P type was this deficiency statistically significant, which would hypothetically implicate an unidentified substrate in the pathophysiology of dietary migraine (8). Finally, still within the frame of the 'amine hypothesis', the possibility that dietary patients could absorb more of the substances due to a deficiency or a change in sensitivity of one or more intestinal-wall enzymes has also been tested (9). Again, results have not consistently confirmed this possibility.

With all these negative results, there has been almost no interest in studying, clinically or pathophysiologically, the relationship between migraine and diet in the last two decades. As just one significant example, both the aminergic hypothesis and IgE-mediated allergy hypothesis have totally disappeared as potential explanations for the pathophysiology of migraine attacks in the last edition of *The Headaches* (10), even though we do continue to see many patients who experience migraine attacks when they eat certain foods or whose migraine improves on some diets (11). In this issue of *Cephalalgia,* Alpay and co-workers report the results of an interesting randomised, double-blind, cross-over, headache diary–based trial with 30 patients having migraine without aura (12). Following a six-week baseline, IgG antibodies against 266 food antigens were determined. Then the investigators randomised the patients to a six-week individualised diet either including or excluding specific foods associated with raised IgG antibodies. Following a two-week diet-free interval after the first period, the same patients were given the opposite diet. Both patients and physicians were blind to the type of diet and IgG tests. Interestingly, most patients seemed to be IgG-positive for several foods and in more than half of these cases titres were graded at least as moderate. Compared to baseline, there was a statistically significant reduction both in the number of headache days and in the number of migraine attacks in the elimination diet period. The results of this Turkish trial are in line with those of a recent Mexican study in which IgG antibodies against 108 food allergens were measured in 56 migraine patients and 56 controls without migraine. IgG antibodies were statistically more frequent in the migraine patients, who then improved on an elimination diet without the need of medication (13).

Even taking into account the limitations of the Turkish trial—the rather low number of patients, relatively short follow-up, potential carry-over effect of a cross-over design, that the positive effects of the diet could be due to non-immunological mechanisms, the specificity and sensitivity of the enzyme-linked immunosorbent assay (ELISA) test and the fact that, due to the short duration of the trial, the authors were unable to correlate the clinical response with a decrease in the level of IgG antibodies—it is true that they offer a rather convincing explanation for dietary migraine, which should be tested in future larger and longer trials.

The interest in a role for IgG antibodies in food allergy has been recently driven by the findings in irritable bowel syndrome (IBS) and functional dyspepsia. Concurring with migraine results, the levels of IgG, and not IgE, antibodies have been shown to be increased in IBS patients and recent studies have found a significant improvement in IBS on elimination diets (14–16). Interestingly, many of the clinical characteristics of IBS are conceptually similar to those of migraine, and subjects with IBS are at higher risk than controls to suffer from migraine (17). One further proof of a role of IgG antibodies against food antigens in the development of migraine attacks is the known association between migraine and celiac disease and the improvements of celiac sufferers' migraine after changing to a gluten-free diet (18).

The mechanisms of IgG-mediated food allergy have not been fully elucidated and remain speculative. It has been proposed that food-allergy antigens transported by way of mast cells activate T helper and B lymphocytes, increasing the production of IgG antibodies and cytokines (19). Then the increased IgG antibodies and cytokines would lead to an inflammation response, which, as pointed out by Alpay and co-workers (11), seems to play an important role in the pathophysiology of migraine attacks. Supporting this hypothesis, a recent study has shown that anti-food IgG antibodies in obese juveniles are associated with systemic inflammation (20). These data are interesting, as obesity seems to be a risk factor in the development of chronic migraine (21). Alternatively, however, elevated IgG antibodies to food could be secondary to 'inflammation' and therefore be more of an epiphenomenon rather than a true delayed allergic reaction. In any case, Alpay and co-workers' results, if fully confirmed in future trials, may be important not only in terms of their obvious consequences for the management of our migraine patients, but also conceptually, as the clarification of the mechanisms through which IgG antibodies are able to lead to development of migraine attacks would improve the knowledge of migraine pathophysiology.

But consequences of these findings could be even more extensive. For instance, the dramatic differences in diet between the Occidental countries, where migraine prevalence is high and almost identical, and African or Asiatic countries, where migraine prevalence is clearly lower, could theoretically explain, at least in part, these epidemiological findings.

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