Revista Alergia México 2007;54(5):162-8

Artículo original

Food allergy mediated by IgG antibodies associated with migraine in adults

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RESUMEN

Introducción: la migraña se presenta con una prevalencia de un 18 %. El tratamiento requiere de medicamentos así como medidas específicas que estarán de acuerdo con la historia clínica. En algunos pacientes, la IgG específica contra alimentos ha sido mencionada en el mecanismo de ésta, pero el estudio serológico ha sido poco estudiado.
Objetivo: el motivo del presente trabajo fue investigar la presencia de anticuerpos tipo IgG contra alimentos en pacientes con migraña refractaria al tratamiento tradicional.
Material y métodos: se investigó la presencia de anticuerpos séricos de tipo IgG contra 108 alimentos usando una prueba inmunoenzimática. Se incluyeron 56 pacientes con migraña y un grupo control sin el padecimiento.
Resultados: además de que la presencia de anticuerpos de tipo IgG contra alimentos fue estadísticamente significativa en los pacientes con migraña cuando se compararon con el grupo control, la eliminación del alimento en la dieta controló la migraña, no habiendo necesidad del uso de medicamentos.
Conclusión: de acuerdo con los resultados obtenidos, la presencia de anticuerpos de tipo IgG contra alimentos, debería de ser incluida en el estudio de pacientes con migraña.
Palabras clave: migraña, alergia, alimentos, anticuerpos IgG.

ABSTRACT

Background: Migraine occurs with a high prevalence of 18 per cent. Management requires a tailored regimen of pharmacological and other measures based on individual clinical history. In some patients, allergen-specific IgG has been suspected to be involved in their mechanism, however, serological methods to investigate such possibility, are seldomly used.
Objective: The aim of this study was to investigate allergen-specific IgG in serum of patients with migraine refractory to traditional treatment.
Material and methods: Serum antibodies to specific 108 food allergens were measured by enzyme immunoassay from 56 patients with migraine and a control group without migraine.
Results: In addition to statistical significant differences in the number of positives for IgG food allergens between patients with migraine and a controlled group, elimination diets successfully control the migraine without the need of medications.
Conclusion: According to the results obtained, serum IgG antibodies to common food should be investigated in patients with migraine.
Key words: Food allergy, migraine, IgG antibodies.

It is estimated that 18 % of women and 6 % of the men have migraine, thus making it a disease of high importance.[1] As many as 30 million Americans suffer migraine headaches and the impact on patients and their families can be tremendous. Also, treatment can present diagnostic and therapeutic challenges. Often, this condition significantly impairs the quality of life and places a large burden on health care resources. Treatment choice for acute migraine should be based on the severity and frequency of headaches, associated symptoms, comorbidities, and a complete good clinical history.[2-4]

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Recibido: agosto, 2007. Aceptado: agosto, 2007.

La versión completa de este artículo también está disponible en internet: **www.revistasmedicasmexicanas.com.mx**

Many years ago, the association of pain and/or inflammation with certain clinical signs, led the physician to suspect a connection between the immunological mechanism and headaches or migraine.[5] In addition, immediate food allergy has been known to produce systemic and organ specific dysfunction that can be IgE mediated. Lately, few investigations reported headache and migraine as a late allergy reaction mediated by IgG, although the majority of severe reactions are mediated via IgE.[5-8]

Migraine epidemiological studies showed that prevalence of this disease is consistently less prevalent in Asians than in Caucasian populations. Migraine in Asians is only 20-50% of that reported in Caucasians.[9]

Migraine is a painful, incapacitating disease that affects a significant portion of the adult population with a substantial economic burden on society. The Disorder is characterized by recurrent unilateral headaches, usually accompanied by nausea, vomiting, photophobia and/or phonofobia. A number of hypotheses have emerged to explain the specific causes of migraine. Current theories suggest a primary central nervous system event. It has been suggested that a mutation in a calcium gene channel renders the individual to be more sensitive towards environmental factors, resulting in a wave of cortical spreading depression when the attacks are initiated, and with a positron emission tomography, an active region has been pointed out in the brainstem.[10]

Food hypersensitivity encompasses any immunologically mediated adverse reaction following the ingestion of a specific food. Despite the confusion and controversy surrounding this area, significant research advances have been made over the past 30 years defining epidemiologic, pathophysiologic, and clinical features of this food reactions.[10-14]

Evidence that foods are involved in headache precipitating factors have been supported on the basis of change in immunoglobulin or complement slit product levels during an attack[15-17] local mast cells degranulation,[18,19] plasma histamine levels,[19,20] circulating immune complexes and T cells increase after local food challenge accompanied by an increase in interluekin-2 release.[21] Finally, it has been found that disturbances of prostaglandin D2 and F2 may alter cerebral blood flow[22] and decreases TNF-RI.[23]

There has been an increase in the prevalence of food allergy, asthma and severe reactions to foods in the past decade. The reason for this increase is unknown and despite the potential for a lethal outcome, no treatments or therapies are available. In the majority of the patients, an IgE mediated food allergy mechanism has been established, however there are cases in which IgG-reactive food elimination diets are helpful in patients with migraine.[24-27]

In the last years, we have focused our investigation on the involvement of IgG antibodies to food, as responsible of a late allergic reaction.

MATERIAL AND METHODS

In the present investigation, patients with recurrent attacks of migraine (at least one a month) were clinically evaluated by a neurologist and received medical treatment, as well as, typical exclusion diets were included. Since migraine is present in patients with other pathology, patients with known allergies, hormonal, neurological or metabolic diseases were excluded. Simultaneously individuals with no allergies, of the same age and gender of as that of the, patients were included as a control group. Venous blood samples were obtained to measure food reactivity in an immunoassay using as a second antibody anti human IgG. The immunoassay analysis was made in Immuno Laboratories, Fort Lauderdale, FL., U.S.A., against 108 food allergens (table 1) that were previously investigated to be the most reactive in different human diseases associated with or without IgE mediated allergy.

Patient's evaluation was made with clinical history, and skin test for IgE mediated allergy. After IgG positive reactivity was reported, all patients were under specific exclusion diet for six months, according to their individual's results, and a specific diet was given to all patients according to test results. At the end of the study, patients were asked to resume consumption of the foods they had been advised to eliminate in order to assess the effects of their

Table 1. Standard food sensitivity immuno assay for IgG

Alfalfa	Cherry	Herring	Parsley	Shrimp
Almond	Chicken	Lamb	Pea	Snapper
Amaranth	Chili pepper	Lemon	Peach	Sole
Apple	Cinnamon	Lentil	Peanut	Soybean
Asparagus	Clam	Lettuce	Pecan	Spinach
Avocado	Clove	Lime	Pepper b/w	Strawberry
Banana	Cocoa-chocolate	Lobster	Pepper green	Sugar
Barley	Coconut	Mackerel	Perch	Sunflower
Bean, kidney	Cod	Milk cow	Pineapple	Tangerine
Beef	Coffee	Milk goat	Plum	Tea
Brazil nut	Corn	Millet	Potato	Tomato
Broccoli	Cranberry	Mung bean	Potato sweet	Tuna
Brussels sprout	Crab	Mushroom	Pork	Turkey
Buckwheat	Egg	Mustard	Pumpkin	Walnut
Cabbage	Eggplant	Nut meg	Radish	Wheat
Cantaloupe	Flounder	Oat	Rape seed	White fish
Carrot	Garlic	Olive	Rice	Yam
Casein	Ginger	Onion	Rye	Yeast bakers
Cashew nut	Grape	Orange	Sage	Yeast brewer
Celery	Grapefruit	Oregano	Salmon	Zucchini
Cauliflower	Haddock	Oyster	Sesame	
Cheese	Halibut	Papaya	Scallops	

reintroduction. During the diet phase of the present investigation, patients were not allowed to take concomitant medication, mainly painkillers. Any patient withdrawing from the diet, were excluded.

Statistical analysis was made with the two-sample *t* test and the Wilcox on Mann-Whitney test.

RESULTS

There were a total of 56 patients with migraine, along with their respective controls. Their age ranged between 35 and 56 years old. Forty-eight patients were females. Clinical history from fourteen patients showed family history of allergies without migraine. IgE skin test was positive in 5 patients for inhalants for tree to four different foods. Immunoassay for food IgG was found in all patients investigated and in fifteen (26%) of the control individuals. The number of positive IgG food reactivity in a single patient was between six and thirty, in contrast with the control group with none or a maximum of four. Positive reactivity for fruits and vegetables are seen in table 2 and for other foods in table 3. The highest reactivity of the patients group was observed with egg, cheese, cow's milk, yeast bakers, wheat, tomato, casein, pork and beans, and for the control group reactions included cow's milk, cheese and egg.

Some of the patients had reactivity with more than seven foods up to thirty. Food reactivity for this group can be seen in table 4. In this group, banana, bean, cheese, egg, cow's milk, mushroom, sugar yeast and wheat, were the most reactive. In three cases, the IgG was similar positive to their reaction to the IgE skin test. However, the number of reactivity in each case was greater for IgG than for IgE.

After one to six months with the specific diet, 43 of the patients reported no migraine; in four patients, decrease of the intensity and frequency was observed and no changes were seen in nine. When statistical analysis was made between patients and control group for the IgG food reactivity, results showed a $p < 0.01$.

Table 2. Positive serum IgG fruit and vegetables reactivity from 56 patients with migraine and 56 non-migraine control group

Food	*P*	*C*	*Food*	*P*	*C*	*Food*	*P*	*C*
Alfalfa	3	0	Cranberry	2	0	Peach	2	0
Apple	0	2	Eggplant	2	0	Pineapple	1	0
Asparagus	2	0	Garlic	4	1	Plum	1	0
Avocado	4	0	Grape	3	2	Potato	3	0
Banana	8	1	Lemon	11	3	Pumpkin	2	0
Bean, kidney	14	3	Lettuce	3	0	Radish	3	0
Broccoli	2	0	Lime	5	0	Soybean	5	2
Brussels sprouts	4	0	Mung bean	1	0	Spinach	6	0
Cabbage	2	0	Mushroom	9	1	Strawberry	7	1
Cantaloupe	4	0	Nutmeg	2	0	Tangerine	4	0
Carrot	2	0	Onion	2	2	Tomato	17	2
Cauliflower	3	0	Orange	12	1	Zucchini	2	0
Cherry	2	0	Papaya	2	0	Cherry	2	0
Chili pepper	13	2	Parsley	1	0	Chili pepper	13	2
Corn	11	2	Pea	1	0	Corn	11	2

P = patient, C = control.

Table 3. Positive serum IgG food reactivity others than fruit and vegetables from 56 patients with migraine and 56 non-migraine control group

Food	*P*	*C*	*Food*	*P*	*C*	*Food*	*P*	*C*
Amaranth	3	0	Herring	2	0	Pork	14	2
Beef	2	0	Lamb	3	0	Rice	9	1
Brazil nut	2	0	Lentil	1	0	Rye	6	1
Casein	15	2	Lobster	2	0	Salmon	1	1
Cashew nut	3	0	Mackerel	2	0	Sesame	4	0
Cheese	24	4	Milk cow	24	4	Shrimp	10	2
Chicken	3	0	Milk goat	8	2	Snapper	2	0
Cinnamon	1	0	Millet	1	0	Sugar	5	1
Clove	1	0	Mustard	6	0	Sunflower	1	0
Cocoa/Chocolate	8	2	Oat	4	0	Tuna	2	0
Coffee	6	2	Oregano	2	0	Walnut	4	1
Crab	4	0	Oyster	2	0	Wheat	19	2
Egg	26	3	Peanut	11	2	White fish	4	1
Ginger	2	0	Pepper b/w	8	2	Yeast bakers	21	2
			Pepper green	3	1	Yeast brewer	12	1

P = patient, C = control.

DISCUSSION

Patients with recurrent migraine refractory to traditional treatment were studied for the presence for IgG food reactive antibodies. After one month of elimination diet, as per test results, 43 out of 65 patients showed a complete remission of their migraine. The association of migraine and food allergy has been known for many years mainly through an IgE mediated mechanism.[5,22-29] However, the association of food IgG mediated disease has been supported by few studies.[6,29-33] In the present study, disease activity was controlled by elimination diet.

Even though the IgG assay was done in the USA, we believe that food allergens between both countries are similar. Today, the origin of many food items

Table 4. Positive serum IgG food reactivity from eleven patients having between seven and thirty food reactivities

Food	*P*	*Food*	*P*	*Food*	*P*	*Food*	*P*
Alfalfa	7,11*	Clove	8	Mushroom	2,4,5,7,8,11	Rye	1,3,7,8
Amaranth	5	Coffee	9,11	Mung bean	2	Sage	8
Asparagus	1,8,11	Corn	1,10	Mustard	8	Sesame	1,8,11
Avocado	9,10	Crab	6	Nut meg	8	Shrimp	6
Banana	1,2,3,6,7,11	Cranberry	4,7	Oat	1,7	Spinach	1,2,3,11
Barley	1	Egg	1,2,4,5,6,8,10	Onion	7	Snapper	2
Bean	4,7,8,10,11	Eggplant	7	Orange	7	Sunflower	8
Broccoli	3	Garlic	7,11	Oregano	8	Sugar	2,4,5,8,11
Brussels sprouts	3,9	Ginger	8	Oyster	8	Tomato	7,11
Cabbage	3	Grape	7	Papaya	3	Tangerine	7,8
Cantaloupe	7	Herring	2	Pepper b/w	1,2,5,7	Tuna	2
Carrot	7	Lemon	7,8,10	Pork	9	Yeast bakers	2,4,6,7,8,10,11
Cashew nut	1,7	Lettuce	1,7	Pineapple	2	Yeast brewer	2,3,4,5,6,7,8,9,11
Cauliflower	3	Lime	7,8	Parsley	3	Wheat	3,7,8,9,10,11
Celery	7	Lentil	2	Pea	7	Walnut	9
Cheese	1,3,4,5,6,8,9,10	Lobster	6	Peach	7	Zucchini	11
Cherry	3	Mackerel	2	Plumb	7		
Chili pepper	9	Milk cow	1,2,3,8,9,10	Pumpkin	2		
Cinnamon	8	Milk goat	1,4,11	Rice	1		
		Millet	1	Radish	3,7		

Every number represents a patient.

in México is not easily identified due to the fact that we can find in any market, meat, milk or vegetables produced in other countries. Therefore, we accept test results without any reservation, although the optimum method of determining a food allergy is by challenging with fresh food,[34] however it's accepted that allergy testing can be done with commercial available purified allergens.

During review of clinical history, we found six patients with migraine and colitis. After a month of specific diet, improvement of both diseases was observed. This result was expected, since it is known that there exists an association of gastrointestinal disease and IgG food hypersensibility.[35-37] Furthermore, food-specific IgG4 antibodies have been demonstrated to be associated with irritable bowel syndrome. The exclusion diet based on IgG4 titers, improved symptoms and is associated with improvement of rectal compliance. In one of the investigations, after 12 weeks diet, a reduction in symptom score was observed in comparison with patients in a sham diet.[36] In addition, research done in dogs, showed that these animals with gastrointestinal disease had more food allergen-specific IgG compared to normal and atopic dogs.[38]

The positive IgG food reactivity seen in the control group is probably difficult to explain, since they did not have any disease or allergy. However, the presence of food reactive IgG antibodies has been observed in healthy individuals. [39-41]

The presence of several reactivities in a serum sample, such as in eleven patients found in the present investigation (Table 4), could be explained due to a cross reactivity with fruit and/or vegetables. This cross reactivity has been demonstrated by immunoblot and immunodot-blot analysis, as well as prick skin test with peanut, soybean, lima bean, pea, and garbanzo bean.[37] Multiple sensitizations to other vegetable products have been observed, whether they come from the same family or taxonomically unrelated, although they do not always share the same clinical expression. The basis of this

association among vegetables foods and with pollens lies within the existence of antibodies against "pan allergens", which determine cross-reactivity. Pan allergens are proteins spread throughout the vegetable kingdom, implicated predominantly in biological functions such as defense mechanism, and consequently, their sequences and structures are highly conserved. They are thermostable and resistance to pepsin digestion, which makes them potent food allergens, thus explaining the frequent development of systemic symptoms.[42-44]

Other important molecules for cross reactivity are the profilins. They are proteins highly conserved in all eukaryotic organisms and present in pollens and a wide variety of vegetable foods.[44-46] However, clinical relevance of cross-reactions based on recognition of carbohydrate determinants and profilin is limited to the population of food or pollen-allergic patients. For selected food allergies however, N-glycans and in specific profiling are of potential clinical relevance.[39] Finally, many plant derived agents contain proteins with tree pollen allergy.[42-45]

Epitope binding patterns of specific food allergens might help to predict which patients will most likely outgrow their food allergy or which patients are clinically tolerant. This may also help to avoid food challenges, which carry a risk for a potentially severe outcome. Research in this field is on the way, showing that IgE and IgG4 epitope mapping by microarray immunoassay revealed diversity of immune response to a specific allergen.[46,47]

Cross reactivity has been observed between pollens and vegetables as well as fruit, therefore, before elimination diet, oral challenges may be important, because has been found that the clinical evaluations and testing was not enough to identify such reactivity.[48,49]

Characterization of cross-reactivity allergens facilitates the study of factors determining clinical relevance of cross-reactivity and possible efficacy of immunotherapy in food allergy. Prescribing therapeutic elimination diets in patients with fruit allergy should include recommendations on which other foods of the same family or group may be safely consumed.

The exclusion of foods to which patients have IgG antibodies might be beneficial in controlling migraines, despite the fact that these antibodies are also present in healthy individuals. The observations that adherence to the diet is critical in determing a good outcome, it is further supported by the observation that the presence of migraine returns few days after the patient reintroduced the food eliminated before the time established in the protocol.

In summary, results from this investigation, support the hypothesis that migraines can be associated with late immunological mechanisms mediated by IgG. Diagnosis was made through an immunoassay and elimination diet of the positive foods, successfully controlling migraines without medication. We suggest that testing for IgG-specific food appears to be helpful in the evaluation of patients with migraine that is refractory to traditional treatment.

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