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# **IgG4 and IgG4-elimination diet in no clinical migraine**

**White Paper**

**(Observational study)**

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## **ABSTRACT**

It is well-known that specific foods trigger migraine attacks in some patients. We aimed to investigate the effect of diet restriction, based on IgG4 antibodies against food antigens on the course of migraine attacks in this preliminary observational study. We have observed that using a IgG4-elimination diet, patients with no clinical migraines were able to reduce the frequency and intensity of the migraine attack, sickness and in one case the completely disappearing of migraines. This study for the first time the possible link between IgG4 and migraines.

## **INTRODUCTION**

The exact pathophysiology of migraine is still unclear. Migraine is characterized by unilateral headache that can be accompanied by nausea/vomiting, photophobia, and/or phonophobia (1) with prevalence of 10-12% in adults, 6% among men, and 15-18% in women (2). Migraine pathogenesis is associated with meningeal inflammation (3,4) beside different genetic mutations, but the mechanism underlying primary migraine still unknown (5). Environmental trigger factors are thought to play an important role. Occurrence of migraine attacks may be triggered by many contributing factors and food is one of the most well-known (3,7). These, however, as with most elements of migraine, need to be individualised to the patient with migraine. Since the 1930s, food allergy and sensitivity (8,9) has been investigated linked to migraine. Few studies showed significant improvement when patients were put on an elimination diet (10,5,6). Non-IgE antibody mediated mechanisms have also been investigated in food allergy (11). Aljada et al.(12) provided evidence for the pro-inflammatory effect of food intake. Immunoglobulin (IgG) antibodies against various food antigens have been reported to be associated with migraine, and the beneficial effect of a diet guided by IgG antibodies to food in migraine patients(13). Accordingly, consumption of IgG-reactive food elimination diets for a specific period provided decrease in headache attacks and significant improvement in symptoms (1). Some foods (such as cheese, chocolate, or wine) are thought to be one of the well-known reasons triggering of migraine attacks according to consistent reports from the patients. Some additives (such as trichloro-galactosucrose or aspartame) may trigger attacks in some migraineurs (4,14). All this is supporting the need for an individualised approach of the diet to relieve migraines that are caused by food via mechanisms (such as histamine-induced vasodilatation) that are not directly involved with the inflammation-induced migraines. IgG antibodies could be one of the markers to identify food which causes inflammation and could cause migraine attacks in predisposed individuals.

Previously the use of the IgG4 antibodies were used to compare IgG4 levels to common food antigens between patients with IBS and healthy controls (15).

In this observational study, we aimed to use our IgG4 antibody test against 74 food allergens in migraines patients and healthy controls to compare the IgG4 levels of common foods, and the possibility to use IgG4-elimination diet (followed by a reintroduction diet) to help managing symptoms.

## **SUBJECTS AND METHODS**

Subjects- 5 people took part to this preliminary observational study (2 as healthy control and 3 with migraines problems), to be aged 33-65 years. All 3 people with migraines were experiencing the same symptoms (with at least 2 migraines/headaches attack per month) for more than 1 year, to be aged 35-60 years, not treated with preventative medications at least two weeks before the testing. Patients who had medication-overuse headache, pure menstrual migraine, or any other associated headache disorder, inflammatory bowel

disease, celiac disease, known lactose intolerance, previous major abdominal surgery, or other significant gastrointestinal disorder were excluded from the study. Patients with drug/alcohol abuse or pregnancy at the time of the study enrolment and during the study were considered as exclusion criteria.

**Measurement of Serum Food Antigen-specific IgG4** - The eligibility of the subjects was determined before the start of the study. Serum food antigen specific IgG4 titres were measured using the Prime100 blood ELISA kit (Healthy Stuff Castle Donington, Derby, DE74 2BZ, United Kingdom). Food allergens are (derived from native foods) immobilized on solid phase (enzyme-linked immunosorbent assay), and IgG4 titres to 74 common foods were measured. Food groups were classified into 10 categories: (1) Fish and seafood, (2) Meats, (3) Grains, (4) Nuts and seeds, (5) Vegetables, (6) Miscellaneous, (7) Egg and dairy, (8) Fruits, (9) Beans, (10) Spices (Table 1). The antibody titres were expressed in U/ml (units per millilitres). The number of subjects with positivity defined as cut-off value  $\geq 0.7$  U/mL.

**Diet preparation** - Diets were arranged according to the IgG4 antibody results; and patients were educated about keeping diet by a certified nutritionist. Diets and food suggestions were given by the nutritionist, trying to offer a nutritionally balanced diet. The elimination diet consisted in the elimination of IgG4-positive food from the diet for four weeks, follow by a reintroduction diet where IgG4-positive foods were reintroduced in the normal diet. Using a reintroduction diet, patients will not eliminate any food nutrient for long period of time and be able to investigate which food can be the possible cause of the symptoms. The reintroduction diet consisted in the reinstate of the triggered foods in the daily diet (one item at time with 3 days distance between each reinstate).

**Data interpretation** - Using the positive results of the IgG4 antibodies for the food antigens (with positivity defined as cut-off value  $\geq 0.7$  U/mL) against the control patients, an elimination diet was administered to the migraine patients after the consultation with a certified nutritionist. A food diary was kept (paper or apps) from the patients during the elimination and reintroduction diet to note how their symptoms changed during the study. The data in terms of intensity and frequency of the migraines attack were summarised and reported.

## **RESULTS**

A total of seven people taken part to this preliminary observational study. In the baseline and during the diet phase, 2 people withdrew from the study (unwilling to follow a diet and busy schedules). The remained five people (2 healthy controls, and 3 migraine patients) completed the blood test for IgG4 food allergens. One of the migraine patients was not able to follow the elimination diet due to medical reason (COVID-19 infection). Ages varied from 33 to 65 (average  $46 \pm 16$  years). All the three migraine patients were experiencing monthly migraine attacks (at least two per months for more than one year) and not taking any preventive medication before the testing. From the IgG4 antibody tests against 74 food allergens, it was observed that 17 foods (Table3) registered a positive response to IgG4 antibodies in patients with migraine against healthy controls (positive response means IgG4 value  $\geq 0.7$  U/mL). The food categories are listed in Table2 from the most frequent IgG4 positivity to the least. Additional research exists linking the benefits of IgG serum testing for migraine headaches when patients present with concurrent conditions such as irritable bowel syndrome (IBS)(5). In this preliminary study we observed that categories as Nuts and seeds, Grains and Dairy are registering high IgG4 value in migraine patients, against controls as previously reported from Aydinlar et al.(5) in the case of IgG.

The two migraine participants that took the IgG4 elimination diet shown reduction in migraine intensity (from 9 to 5 considering a scale 1-10) and in one case the migraine completely disappear gaining more energy, as reported in Table4. The use of the reintroduction

diet helped the participants to reintroduce the triggered food/s back in their diet without eliminating any essential nutrients from their diet, and help them find the right amount that can be consumed without reinstating migraine symptoms.

These preliminary data have shown that it seems to be a sort of link between migraine and IgG4-elimination diet that could help the management of no clinical migraine symptoms. For the first time we are showing that not only the IgG antibodies can be link to migraine but that also IgG4 and IgG4-elimination diet could help migraine patients to manage symptoms and reduce the intensity of migraine attack, improving their quality of life.

## **DISCUSSION and CONCLUSIONS**

Despite the mechanisms of IgG-mediated food reactions have not been fully elucidated, increase in the production of IgG antibodies and cytokines (16) via food allergy antigens has been reported to result in an inflammation response that seems to play an important role in the pathophysiology of migraine attacks (17). In this preliminary observational study, we are investigating for the first time the possibility to use specific IgG antibodies (IgG4) and the IgG4-based elimination diet to improve migraines. We observed that using the IgG4 antibodies similar results in terms of the food categories and frequency of immunoglobulin G4 positivity in migraine patients were obtained, comparing previous published work on the use of IgG and IgG-based elimination diet to improve migraines and IBS symptoms (1,5). Efficacy of IgG4-based elimination diet on patients with not clinical migraines was observed with a reduction in terms of migraines attacks number and intensity.

Use of exclusion diets tailored to the individual patient based on the serum IgG antibody titres has been reported to have many advantages, including higher patient compliance and physician confidence, and individualization of the diet to a given patient, thereby obviating the need for excluding a large number of foods from the diet (5). Our findings indicate that food elimination based on IgG4 antibodies in no clinical migraine patients may effectively reduce their symptoms. The use of a reintroduction diet shown the possibility to investigate which particular food could be part of the cause of symptoms and see if the consumption of small doses of trigger food can be tolerated from the patient without the elimination of any essential nutrients in the diet.

These preliminary results demonstrated that there is possibility to use IgG4 antibodies and IgG4-based elimination diet for the management and improvement of migraines in no clinical cases. We have demonstrated that using our testing for IgG4 antibodies people with no clinical migraines could possibly use an IgG4 elimination diet (under the supervision and supported by a registered nutritionist), that could help managing symptoms and improve their health.

***Due to the small number of participants to this preliminary study and to support our findings, we want to continue this study increasing the number of people with not clinical migraines (with the help of medical clinics for the referral of those patients) and extend the study up to six months with an elimination diet of 3 months follow by a reintroduction diet. In this way we will be able to collect more data and understand better the role of IgG4 and the use of IgG4 elimination diet for no clinical migraine patients. A further study/investigation is needed to underpin the link between IgG antibody and specifically IgG4-elimination diet for the management of symptoms in no clinical migraine patients, as possible cost-effective alternatives to conventional approaches (medications as pain killers).***



**Table1: Full list of 74 allergens divided by categories tested**

<b>LIST OF THE 74 ALLERGENS TESTED USING IgG4 ANTIBODIES IN THIS STUDY</b>			
<b>Fish and Seafood:</b> Salmon, Cod, Plaice Squid, Blue mussels, Octopus, Tuna, Trout, Sunflower seeds, Pollock, Herring, Shrimp Oyster	<b>Meats:</b> Pork, Beef, Lamb, Chicken, Duck, Turkey	<b>Grains:</b> Wheat, Oat, Splet, Rye, Buckwheat, Barley, Durum wheat, Rice	<b>Nuts and Seeds:</b> Sesame, Almond, Hazelnut, Peanut, Pistacio, Cashew, Pumpkin seeds
<b>Miscellaneous:</b> Baker's yeats, Gluten, Mustard, Coffee, Cocoa	<b>Egg and Dairy:</b> Egg white/yolk, Guuda Cheese, Casein, Cow's milk, Sheep's milk, Goat milk	<b>Vegetables:</b> Carrot, Cucumber, Broccoli, Garlie, Maize, Cabbage, Celery, Potato, Tomato, Olives, Onion, Button Mushrom	<b>Fruits:</b> Apple. Orange, Grape, Peach, Bannana, Kiwi, Lemon, Pineapple, Strawberry
<b>Beans:</b> Soy, Lentil, Pea green, Bean green	<b>Spices:</b> Egg white/yolk, Guuda Cheese, Casein, Cow's milk, Sheep's milk, Goat milk		

**Table2: The food categories from most to least frequent Immunoglobulin G4 positivity in migraine patients.**

<b>CATEGORIES:</b>	<b>%</b>	<b>NUMBER OF PATIENTS WITH POSITIVE IgG4 TEST</b>
Fish	100%	3
Nuts and seeds	100%	3
Vegetables	66%	2
Dairy and egg	66%	2
Beans	66%	2
Grains	33%	1

**Table3: Levels of food specific IgG4 (U/ml  $\pm$  SD) against food antigens between migraine patients and healthy controls.**

ANITGENS	PATIENTS IgG4 U/ml	CONTROL IgG4 U/ml
Almond	19.2 $\pm$ 31.8	1.3 $\pm$ 1.4
Hazelnut	17.3 $\pm$ 28.3	1.6 $\pm$ 1.8
Peanut	1.7 $\pm$ 1.2	0.6 $\pm$ 0.4
Cashew	8.7 $\pm$ 8.7	2.3 $\pm$ 2.8
Cucumber	0.9 $\pm$ 0.9	0.35 $\pm$ 0.0
Cabbage	0.9 $\pm$ 0.7	0.35 $\pm$ 0.0
Salmon	1.5 $\pm$ 0.7	0.35 $\pm$ 0.0
Oat	1.9 $\pm$ 1.6	0.35 $\pm$ 0.0
Wheat	100 $\pm$ 0.0	0.35 $\pm$ 0.0
Spelt	100 $\pm$ 0.0	0.35 $\pm$ 0.0
Barley	14.1 $\pm$ 0.0	0.35 $\pm$ 0.0
Rye	3.5 $\pm$ 0.0	0.35 $\pm$ 0.0
Beef	4.8 $\pm$ 7.0	0.35 $\pm$ 0.0
Egg yolk	6.8 $\pm$ 9.3	0.6 $\pm$ 0.2
Casein	34.4 $\pm$ 56.8	0.35 $\pm$ 0.0
Gouda cheese	34.6 $\pm$ 56.8	0.35 $\pm$ 0.0
Soybeans	1.1 $\pm$ 0.7	0.35 $\pm$ 0.0

**Table4: Summary of the migraine symptoms before and after the IgG4-elimination diet.**

PARTICIPANTS	BEFORE IgG4 DIET	AFTER IgG4 DIET
<b>Patient 1 (migraine)</b>	2 migraines attack per month, intensity 8-9 (scale 1-10), sickness	No migraines, no sickness, more energy
<b>Patient 2 (migraine)</b>	2-5 migraines attack per month, intensity 9 (scale 1-10)	2-3 migraines attack per month, intensity 5-6 (scale 1-10)

## **REFERENCES**

1. Arroyave Hernández CM, Echavarría Pinto M, Hernández Montiel HL. Food allergy mediated by IgG antibodies associated with migraine in adults. *Rev Alerg Mex.* 2007; 54:162-168.
2. Rasmussen BK. Epidemiology of headache. *Cephalalgia.* 2001;21:774-777.
3. Diamond S, Prager J, Freitag FG. Diet and headache. Is there a link? *Postgrad Med J* 1986; 79: 279–286.
4. Millichap JG, Yee MM. The diet factor in paediatric and adolescent migraine. *Pediatr Neurol* 2003; 28: 9–15.
5. Aydinlar EI, Dikmen PY, Tiftikci A, Saruc M, Aksu M, Gunsoy HG, Tozun N. IgG-Based Elimination Diet in Migraine Plus Irritable Bowel Syndrome. *Headache.* 2013; 53(3):514-25.
6. Alpay K; Ertas M; Orhan EK; Ustay DK; Lieners C; Baykan B. Diet restriction in migraine, based on IgG against foods: a clinical double-blind, randomised, cross-over trial. *Cephalalgia* 2010; 30(7): 829-37.
7. Vaughan TR. The role of food in the pathogenesis of migraine headache. *Clin Rev Allergy* 1994; 12: 167–180.
8. Diamond S, Prager J, Freitag FG. Diet and headache. Is there a link? *Postgrad Med J.* 1986;79:279- 286
9. Peatfield RC, Glover V, Littlewood JT, Sandler M, Clifford Rose F. The prevalence of diet-induced migraine. *Cephalalgia.* 1984;4:179-183.
10. Balyeat RM, Brittain FL. Allergic migraine: based on the study of fifty-five cases. *Am J Med Sci* 1930; 180: 212–221.
11. Halpern GM, Scott JR. Non-IgE antibody mediated mechanisms in food allergy. *Ann Allergy* 1987; 58: 14–27
12. Aljada A, Mohanty P, Ghanim H, et al. Increase in intranuclear nuclear factor kappaB and decrease in inhibitor kappaB in mononuclear cells after a mixed meal: evidence for a proinflammatory effect. *Am J Clin Nutr* 2004; 79: 682–690.
13. Rees T, Watson D. A prospective audit of food intolerance among migraine patients in primary care clinical practice. *Headache Care* 2005; 2: 11–14.
14. Bigal ME, Krymchantowski AV. Migraine triggered by sucralose – a case report. *Headache* 2006; 46: 515–517.
15. Hong SL and Kwang JL. Alterations of Food-specific Serum IgG4 Titers to Common Food Antigens in Patients With Irritable Bowel Syndrome. *J Neurogastroenterol Motil* 2017; 23:578-584
16. Bischoff SC, Crowe SE. Gastrointestinal food allergy: New insights into pathophysiology and clinical perspectives. *Gastroenterology.* 2005;128:1089- 1113.
17. Pascual J, Leno C. A woman with daily headaches. *J Headache Pain.* 2005;6:91-92.