

Research Article / Araştırma Makalesi

Does Food Elimination Based on Immunoglobulin G Antibodies Diminish Tension-Type Headache? A Randomised Cross - Over Study
İmmünoglobulin G Antikorlarına Dayalı Gıda Eliminasyonu Gerilim Tipi Baş Ağrısını Azaltır Mı? –Randomize Çapraz Çalışma

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Abstract: The aim was to evaluate if foods, against which patient has IgG antibodies, trigger tension type headache (TTH). 22 patients (8 male, 14 female; 8 chronic TTH, 14 frequent episodic TTH) were recruited. The study had four periods: cooperation, provocation, free diet month and elimination were determined. At the cooperation period patients' cooperation abilities were checked. All patients were screened for 271 different antibodies against foods using Imupro300. Thus a list of food sensitivity was described for each patient. In provocation period, those detected foods were added to diet. In elimination period, those foods were eliminated from the diet with false foods added. In free diet month, there were no restrictions. Patients recorded the number of the days with headache as well as headache frequency, severity and duration and analgesic intake. These headache features in cooperation, provocation and elimination periods were compared. In the elimination period there was a significant decrease in the number of days with headache, headache frequency and duration in all patients. A significant increase in these three features were observed in the provocation period. In chronic TTH patients, only the number of the days with headache significantly increased in provocation period. IgG antibodies against foods may have a role in TTH. Number of days with headache, headache frequency and duration can be decreased by eliminating related foods from the diet, and this can be a part of the treatment. IgG antibodies against foods may be one of the pathophysiological mechanisms triggering TTH.

Keywords: Tension type headache, IgG, Food allergy

Özet: Bu çalışmanın amacı, hastada IgG antikorlu bulunan besinlerin gerilim tipi baş ağrısını (GTBA) tetikleyip tetiklemediğini değerlendirmektir. Toplam 22 hasta (8 erkek, 14 kadın; 8 kronik GTBA, 14 sık epizodik GTBA) çalışmaya alındı. Çalışmanın dört dönemi vardı: kooperasyon, provokasyon, serbest dönem ve eliminasyon dönemi. Kooperasyon döneminde hastaların kooperasyon yetenekleri kontrol edildi. Tüm hastalar, Imupro300 kullanılarak gıdalara karşı 271 farklı antikor açısından tarandı ve her hasta için bir besin duyarlılığı listesi tanımlandı. Provokasyon döneminde tespit edilen besinler diyeteye eklendi. Eliminasyon döneminde hastanın antikorlu olmayan besinler diyeteye eklenerek alerjik besinler diyetten çıkarıldı. Serbest diyet ayında herhangi bir kısıtlama yoktu. Hastalar baş ağrısının olduğu gün sayısını, baş ağrısının sıklığını, şiddetini ve süresini ve analjezik alımını kaydetti. Kooperasyon, provokasyon ve eliminasyon dönemlerindeki bu baş ağrısı özellikleri karşılaştırıldı. Eliminasyon periyodunda tüm hastalarda baş ağrısı olan gün sayısında, baş ağrısı sıklığında ve süresinde anlamlı azalma oldu. Provokasyon döneminde bu üç özellikte de önemli bir artış gözlemlendi. Kronik GTBA hastalarında provokasyon döneminde sadece baş ağrısı olan gün sayısı anlamlı olarak arttı. Gıdalara karşı IgG antikorlarının GTBA'da rolü olabilir. İlgili besinlerin diyetten çıkarılmasıyla baş ağrılı gün sayısı, baş ağrısı sıklığı ve süresi azaltılabilir ve bu tedavinin bir parçası olabilir. Gıdalara karşı IgG antikorları, GTBA'yı tetikleyen patofizyolojik mekanizmalardan biri olabilir.

Anahtar Kelimeler: Gerilim tipi baş ağrısı, IgG, Gıda alerjisi

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1. Introduction

Tension-type headache (TTH) is the most common type of headache in all age groups with a lifetime prevalence of 30-78% (1). The one year prevalence of chronic TTH is 0.5-4.8% whereas prevalence of episodic TTH is 38% (2,3). Yet there are many patients who do not consult a physician for this disease, and this leads to TTH being an underdiagnosed disease. Although headache severity is less than migraine, TTH affects quality of life, and causes productive time and paid work loss (4,5). However, the studies on triggering factors and pathogenesis are very few and pathophysiology of the disease is unclear.

Despite the role of IgE mediated systemic inflammation in the diseases have been showed by many studies before, IgG mediated late inflammation (also called IgG mediated food intolerance) has gained popularity in the past decade with in vivo and in vitro immunologic studies. Being exposed to little amounts of specific foods repeatedly cause IgG mediated late onset inflammation and this inflammation is considered to be associated with diseases. The relationship between headache and inflammation has been researched for a while now.

Some of the studies suggest that migraine and TTH share a common pathophysiological process with TTH being a less severe form of migraine (6). A may play a role in the pathogenesis of TTH (7). However, to the best of our knowledge there are no studies about IgG type food intolerance triggering TTH.

The aim of this study was to search whether IgG antibodies against foods are also responsible for TTH.

2. Materials and Methods

Experimental protocol-- After obtaining consent from the local ethics committee and the individuals, frequent episodic and chronic tension type headache (TTH) patients were enrolled. Diagnoses were made according to the criteria of the International Classification of Headache Disorders, 2nd edition (1). Patients (i) aged between 18-55 years, (ii) with no coexisting diseases, (iii) with no preventive medication use for the last three

months, (iv) with no medication overuse history, (v) cooperable for dietary restrictions and the headache diary. Overall 22 patients (8 male, 14 female) were recruited. Eight of the patients had chronic TTH and 14 had frequent episodic TTH. All of the patients were examined by the same physician (FND, author) throughout the study. All recruited patients signed an informed consent form.

The study consisted of four periods; cooperation, provocation, elimination, and a free diet month between provocation and elimination periods. Each period lasted one month. The order of the periods were known by the dietician whereas patients and the physician were blind. Patients recorded their headache features in a diary. Diary included number of the days with headache, headache frequency, severity, duration and analgesics consumed.

Follow-up

In cooperation period, patients were given a certain diet which in fact compatible to the individual daily eating habit. This first period was included to assure observing patients' cooperability to the study –namely to the diet and the headache diary-. Patients unable to cooperate or who appeared not to have TTH were not included in the study. In provocation period the diet contained the foods against which they had IgG antibodies. The amount of these foods were decided empirically by the dietician. For instance the requested amount was two portions a week for fish whereas a slice of bread in every meal. However the diet contained at least one food with IgG a day. Patients were allowed to eat as they preferred during the free diet month. In elimination period patients were given a diet eliminating all foods, against which they had IgG antibodies, from the diet. For example if the patient had IgG antibody against wheat, all foods including wheat were eliminated from the diet. To avoid recognition of the periods by the patient or the clinician, at least two other foods against IgG antibodies were negative, were either restricted or promoted during provocation and elimination periods, respectively. Diets were designed by a dietician.

Headache severity was evaluated with Visual Analog Scale (VAS). We empirically obtained a headache burden by multiplying three headache features (number of the days with headache, headache severity and duration). Each headache feature and the headache burden in three periods were compared.

Detection of IgG antibodies against food antigens

After the cooperation period, each patient's venous blood sample was tested by an enzyme linked immunosorbant assay (ELISA) test (ImuPro 300 test; Evomed/ R-Biopharm AG, Darmstadt, Germany) for IgG antibodies against 271 different food antigens. Cut-off value of IgG concentration was 7.50 µg/ml. The physician and patients were not informed about the results throughout the study.

Statistical methods

Friedman Test was used to compare three periods (cooperation, provocation and elimination).

Classification of evidence—This randomized, double-blind, cross-over trial provides Class III evidence that IgG antibodies against food antigens have a role in TTH.

3. Results

Thirty patients (8 male, 14 female) were recruited for this study. Eight of them had chronic TTH and 14 (63,6%) had frequent episodic TTH. The mean age of the patients was 36.7 (±8.7) years (22-53). Mean headache duration was 8.1 (±7.8) years (1-30). At least six IgG antibodies against food antigens were detected in each patient (6-40 IgG antibodies mean:18.53 SD (±11,90). There was at least

grade 1 reactions to 103 of out of a total of a 271 foods. The most positive result was 'fermented cow cheese', other common foods were 'chicken eggs, cow's milk, curdled dairy products made from cow's milk, kefir, baked milk, Ricotta cheese, oats, halloumi cheese, goat and sheep milk and chesse, barley, wheat, rye and, gluten'. It was noted that a patient may be sensitive to more than one food antigen at the same time. Table 1 shows a list of the foods against which patients had IgG antibodies.

There was a significant decrease in the number of days with headache, headache frequency, duration and headache burden in elimination period compared with both cooperation and provocation periods. (Table 2) During provocation period there was a significant increase in the number of days with headache, headache frequency, duration and headache burden compared with both elimination and cooperation periods. Analgesic intake was increased at provocation and decreased at elimination period. No significant change in headache severity was found between three periods.

The statistical analysis of 14 out of 22 patients who had frequent episodic TTH presented exactly the same statistical differences as 22 TTH patients. However, eight chronic TTH patients only revealed a significant increase in the number of the days with headache and headache burden in provocation period compared with elimination and cooperation periods. For the eight chronic TTH patients there weren't any significant difference in headache duration or severity and analgesic intake between the periods.

Table 1. IgG antibodies against food antigens and the number of patients with a positive test (in 22 TTH patients)

Food	Positive test
Cheese made from fermented milk (Sour-milk products)	17
Chicken egg	15
Milk (cow)	13
Sour-milk products (cow)	12
Kefir, milk cooked, Ricotta cheese, oat	11
Halloumi, sheep milk and cheese, wheat, rye	10

Barley, gluten, kamut, spelt,	9
Poppy seeds	8
Sesame, Sunflower seed, quail eggs	7
Sweet pepper, akaju peanut,	6
Antep peanut,kiwi, tomato, green pepper	5
Black pepper, guar flour (E412) , apple,banana, chickpeas, Pistachio, walnut, apple, hazelnut, cherry, agar-agar (E406),	4
Plum, orange, vanilla, pumpkin seeds, cashew karnel, cocoa bean, flaxseed, chili cayenne, peanut	3
Lentil, broad bean, lemon, pear, peach, cinnamon, yeast, tuna fish, goose egg, beet, walnut,chicken, beef, tujna fish, peppermint, Red cabbage	2
Celery, olive, potato, aubergine, green pea, watermelon, nectarine, pectin (E440), honey (mixture), linseed, chili cayenne, cucumber, artichoke, green bean, strawberry, soya bean, thyme, garlic, beef, parsley, Beetroot, pumpkin, raspberry, quince, blackberry, white cabbage, grapefruit, honeydew melon, apricot, mandarin, pomegranate, fig, mustard seed, turkey hen, salmon, almond, mushroom, octopus, coffee, black tea, jerusalem artichoke, iceberg lettuce, sweet chestnut, Grapefruit, Aspergillus niger, ocean perch, trout, ginger, Brussels sprout, maize, sweet corn, aniseed, red radish, white radish, buckwheat, cane sugar, chili habanero, chili jalapeno, rice, spinach, mango, broccoli, carrot, anchovy, leek, blue mussels, cumin, gilthead bream, carob	1

Table 2. The change of the headache parameters with diet phases

		Cooperation phase (mean±SD)	Elimination phase (mean±SD)	Provocation phase (mean±SD)	P values (Friedman test)
Number of days with headache in 30 days	All patients (n=22)	11.72±5.63	7,13±5.10	14.45±6.32	<0.0001
	Frequent TTH (n=14)	8.59±2.48	5.04±2.14	11.5±4.62	<0.0001
	Chronic TTH (n=8)	18.5±2.44	12.5±4.47	21.12±1.80	0.02
Mean attack severity (VAS)*	All patients (n=22)	5.08±0.77	4.75±1.06	5.43±1.07	0.05
	Frequent TTH (n=14)	5.04±0.85	4.42±1.04	5.51±1.07	0.07
	Chronic TTH (n=8)	4.90±0.56	4.70±1.09	5.17±0.54	0.565
Mean headache duration in each attack	All patients (n=22)	8.01±3.27	6.18±2.61	9.39±3.23	<0.0001
	Frequent TTH (n=14)	6.03±3.19	4.98±2.14	7.88±3.51	<0.0001
	Chronic TTH (n=8)	9.3±2.48	8.36±1.80	10.37±2.19	0.072
Mean Daily analgesic intake (number of tablets)	All patients (n=22)	0.72±1.54	0.81±1.91	1.77±2.22	<0.0001
	Frequent TTH (n=14)	0.72±1.31	0.13±0.35	2.18±1.76	<0.0001
	Chronic TTH (n=8)	1.25±2.05	2.12±2.79	1.87±2.94	0.424
Headache burden	All patients (n=22)	489.58±310.59	249.44±235.34	739.49±417.06	<0.0001
	Frequent TTH (n=14)	275.56±154.07	125.82±111.02	506.65±309.86	<0.0001
	Chronic TTH (n=8)	834.0.5±175.33	485.46±199.14	1132±266.84	0.01

*VAS: visual analog scale *TTH: tension-type headache

4. Discussion

This study suggests an association between high levels of IgG antibodies against food antigens and TTH. We found that when the foods against which the individual had IgG antibodies, were eliminated from the diet, there was a decrease in number of the days with headache, headache duration and analgesic intake, and vice versa. This indicates that IgG antibodies against food antigens may play a role in mechanisms underlying TTH.

To the best of our knowledge there hasn't been any studies addressing IgG antibodies against food antigens in TTH.

Testing for IgG antibodies against food antigens is becoming more popular every day. The association of IgG antibodies against food antigens with obesity, migraine and irritable bowel syndrome (IBS) has been investigated. A recent study by Alpay et al. suggested that eliminating foods -against which the patient has IgG antibodies- from the patient's diet decreased migraine frequency (8). Another study by Arroyave Hernandez et al. showed that migraine patients had IgG antibodies against food antigens more frequently than healthy controls. When detected foods were eliminated from the diet for one month headache episodes ceased in 76% of the patients (9). Aydinlar et al screened the patients who have both migraine and IBS for IgG antibodies against food antigens (10). They reported that by the elimination of the relevant foods migraine attack count, duration, and severity with analgesics need, and also IBS symptoms significantly decreased. Egger et al. reported that oligoantigenic diet helped patients' headache, asthma, eczema and abdominal pain (11). 93% of the patients with headache showed improvement. Rees et al. studied migraine patients for IgG antibodies against food antigens and applied an elimination diet accordingly. They found improvement in 30% of the patients in the first month, and 40% of the patients in the second month. 60% of the patients who got better with the diet, stated that their headaches re-appeared after they started their casual regimen (12). On the other hand a study by Mitchell et al. found no

improvement in migraine attacks with an elimination diet based on the IgG results of the migraine patients (13).

Headache parameters of the eight chronic TTH patients also showed a tendency to decrease with elimination and increase with provocation in our study. However the differences here are not significant possibly due to the small number of patients. On the other hand the pathogenesis of chronic TTH may differ from the frequent episodic TTH.

There wasn't a change in headache severity between three periods. This is in line with the results of Alpay et al.'s study (9) It can be concluded that although foods may trigger headache they do not effect the severity.

Migraine and TTH are suggested to have a common pathogenesis rather than separate clinical entities. In 1973 Waters described this hypothesis according to the clinical observations about dynamic nature of headaches and also from epidemiological datas (14). Thus TTH and migraine with aura are two ends of a clinical spectrum, and migraine without aura places between them (15,16). This is called convergence hypothesis. Studies show similarity of the patient demographics, trigger factors, signs and symptoms of pre-headache phases as well as positive response to same therapeutic agents (16,17). Moreover there is a transition from TTH to migraine or vice versa in some patients or these two entities may present together. The limitation in this study, we did not objectively measured the other potential factors contributing to TTH, such as stress, sleep patterns, and environmental triggers. Also studies with migraine patients and healthy controls comparing TTH with larger number of patients will be more guiding to this issue.

5. Conclusion

This study shows that daily eating habits are amongst the important triggering factors of TTH. The study also indicates that TTH may have an immunologic pathophysiology. The results may help us to treat TTH patients more

successfully. A proper diet extends headache-free periods, diminishes the headache frequency and decreases the analgesic

consumption all of which improves quality of life.

REFERENCES

1. Headache Classification Committee of the International Headache Society (IHS). The International Classification of Headache Disorders, 3rd edition (beta version). *Cephalalgia*. 2013;33(9):629-808.
2. Yu S1, Han X. Update of chronic tension-type headache. *Curr Pain Headache Rep*. 2015;19(1):469.
3. Crystal SC, Robbins MS. Epidemiology of tension-type headache. *Curr Pain Headache Rep*. 2010;14(6):449-54.
4. Steiner TJ, Birbeck GL, Jensen RH, Katsarava Z, Stovner LJ, Martelletti P. Headache disorders are third cause of disability worldwide. *J Headache Pain*. 2015;16:58.
5. Ayzenberg I, Katsarava Z, Sborowski A, Chernysh M, Osipova V, Tabeeva G, Steiner TJ. Headache-attributed burden and its impact on productivity and quality of life in Russia: structured healthcare for headache is urgently needed. *Eur J Neurol*. 2014;21(5):758-65.
6. Cady RK. The Convergence Hypothesis. *Headache*. 2007 Apr;47 Suppl 1:S44-51.
7. İrkeç C, Batur HZ, Aksoy O, Doğanay H. The Neuroimmunologic Approach to Tension Type Headache and Migraine. *Journal of Neurological Sciences (Turkish)*. 2006;12(2): 129-133.
8. 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.
9. 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(5):162-8.
10. Aydınlar EI, Diken PY, Tiftikçi 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.
11. Egger J, Carter CM, Wilson J, Turner MW, Soothill JF. Is migraine food allergy? A double-blind controlled trial of oligoantigenic diet treatment. *Lancet*. 1983;2(8355):865-9.
12. Rees T, Watson D, Lipscombe S, Speight H, Cousins P, Hardman G, Dowson AJ. A prospective audit of food intolerance among migraine patients in primary care clinical practice. *Headache Care*. 2005 June vol2,no2. pp105-110(6).
13. Mitchell N, Hewitt CE, Jayakody, Islam M, Adamson J, Watt I, Torgerson DJ. Randomised controlled trial of food elimination diet based on IgG antibodies for the prevention of migraine like headaches. *Nutrition Journal* 2011 ;10:85.
14. Waters WE. The epidemiological enigma of migraine. *Int J Epidemiol*. 1973;2:189-194.
15. Cady RK, Gutterman DL, Sainers JA, Beach ME. Responsiveness of non-IHS migraine and tension-type headache to sumatriptan. *Cephalalgia* 1997; 17:588-90.
16. Karli N, Zarifoglu M, Calisir N, Akgoz S. Comparison of pre-headache phases and trigger factors of migraine and episodic tension-type headache: do they share similar clinical pathophysiology. *Cephalalgia*. 2005 ;25(6):444-51
17. Cady R, Schreiber C, Farmer K, Sheftell F. Primary headaches: a convergence hypothesis. *Headache*. 2002; 42(3):204-16.

Ethics

Ethics Committee Approval: The study was approved by Ankara University Clinical Research Ethical Committee (Decision no:29-636, Date: 25.04.2011).

Informed Consent: The authors declared that it was not considered necessary to get consent from the patients because the study was a retrospective data analysis.

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