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Is Individualized Diet Restriction Based on IgG Against Foods Effective for Reducing Migraine Frequency in Adults Who Suffer from Migraines?

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ABSTRACT

Objective: The objective of this selective EBM review is to determine whether or not individualized diet restriction based on IgG against foods is effective as migraine prophylaxis in adults who suffer from migraines.

Study Design: Systematic review of three English language primary studies, published between 2009-2011.

Data Sources: Two randomized controlled trials and one case report published after 1996 comparing migraine frequency before and after diet elimination based on IgG against foods were obtained using PubMed and Cochrane databases.

Outcomes Measured: Migraine frequency, recorded by patients in a headache diary throughout the duration of the diet, was the primary outcome measured. Subjects reported baseline migraine frequency and characteristics through a baseline diet phase[6] or through a focused questionnaire,[8] and results were compared after the completion of the diet phase.

Results: None of the studies reported any intervention-related adverse events or side effects. Alpay and colleagues showed a statistically significant reduction in the number of headache days and migraine attacks,[6] with a NNT of 34. Mitchell and colleagues showed a statistically significant reduction in migraine frequency at week 4 of the elimination diet, but after a full 12 weeks, the difference was not statistically significant.[8] In a case report by Nelson-Dooley,[9] the patient showed a subjective reduction of migraine frequency compared to baseline.

Conclusions: Some reduction of migraine frequency was demonstrated by all three studies, however the evidence is inconclusive. This can be attributed to a statistically significant reduction in migraine frequency but a high NNT in the study by Alpay and colleagues, conflicting evidence (migraine frequency at 4 weeks vs. 12 weeks) in the study by Mitchell and colleagues, and the multiple simultaneous treatment interventions and subjective results in the case report by Nelson-Dooley. Larger studies with a longer intervention period ($\geq$4 weeks), emphasizing more controlled diets/meal plans and elimination of confounding factors may clarify these inconsistent study results. Thus, future study is warranted to evaluate prophylactic diet elimination based on IgG against foods for migraine frequency reduction before routine use is recommended.

Key Words: migraine prophylaxis, diet restriction, food elimination, IgG

INTRODUCTION

Migraine is a highly prevalent episodic headache disorder, which presents as a unilateral, throbbing head pain beginning in childhood, or more commonly in adolescence or early adulthood[1]. It affects approximately 15% of females and 6% of males every year and accounts for the second most common cause of headache.[2] Not only does it causes a disabling effect on quality of life for migraine sufferers, but requires approximately 4-6 days of bed rest per year.[8] In the United States, migraine costs estimate as much as $17 billion annually, which is the sum of outpatient visits, medications, laboratory and diagnostic services, management of side effects, and lost productivity in the workplace.[3] The total number of healthcare visits yearly worldwide has not been quantified; however, patients average 2.78 doctor/clinic visits, 0.53 emergency department visits, and 0.06 hospital admissions annually.[4]

Symptoms of migraine include an episodic headache that is unilateral, throbbing, and aggravated by movement which can last for hours to days. It can be associated with specific features, such as phonophobia, photophobia, nausea, and vomiting. In 20-25% of patients, the headache is preceded by an aura, which is a visual disturbance often characterized by flashing lights or zigzag lines.[2]

Currently, there is no unifying theory regarding the pathogenesis of migraine, and the etiology is not completely understood. It appears to be multifactorial in nature, and may be related to emotional state, genetics, vascular factors, trigeminal activation, serotonin imbalance, hormonal changes, and various triggers[1] that may ultimately lead to an inflammatory response in the meninges.[5] Such triggers have yet to be definitively identified, but they may include excess or withdrawal of caffeine, changes in barometric pressure, bright lights or loud sounds, hunger, stress, physical exertion, lack of sleep, and specific dietary items.[2] Specific foods that have been

linked to migraines in some patients include peanuts, oranges, tomatoes, onions, fatty foods, and foods high in tyramine, including but not limited to red wine, chocolate, cheese, and processed meats. However, controlled trials have proved these associations with specific foods invalid.[1]

Because the pathophysiology is not completely understood, various treatments are currently being used for migraine, including abortive and prophylactic treatments. Abortive treatment is indicated at the onset of migraine symptoms, and the most effective current therapy includes triptans/5-HT1 agonists (e.g. sumatriptan, zolmitriptan, naratriptan) and ergot alkaloids (e.g. ergotamine, dihydroergotamine)[1]. Other symptomatic treatment includes opioid analgesics, NSAIDs, aspirin, barbiturates, and antiemetics. Prophylactic measures include beta blockers (eg. propranolol, timolol), antiepileptic medications (eg. divalproex, topiramate), and botulinum toxin injections. Additional treatments include calcium channel blockers, tricyclic antidepressants, and selective serotonin reuptake inhibitors (SSRIs).[3] Further prophylaxis includes behavior modification, including avoidance of triggers including foods and limiting caffeine intake. Chiropractic manipulation, meditation, acupuncture, and biofeedback may also be beneficial in effective migraine prophylaxis.[1]

Such prophylactic measures need to be tailored to each patient depending on the individual identified triggers and exacerbating factors. The success rate of current prophylactic methods is inadequate in many migraine sufferers, and thus studying the individual triggers is appropriate to attempt to reduce attack frequency. Hidden food allergy has been linked to migraine since the 1930s.[6] Early studies showed food elimination to be successful in preventing migraines, and more recent research suggests that food intolerance or hypersensitivity may precipitate migraine attacks.[7] Clinically, food hypersensitivity is often determined empirically, by elimination and challenge diets of suspected foods. However, this process has many

limitations for practitioners, as it is time consuming and challenging to test all existing food combinations. A newer alternative is to test for food specific IgG antibodies to particular foods through a blood test called Enzyme Linked Immuno-Sorbent Assay (ELISA). Positive IgG antibodies to specific foods may indicate a patient's hypersensitivity to those foods. All IgG subclasses, with the exception of IgG4, begin an inflammatory reaction when the antigen is introduced.[6] Theoretically, food with hypersensitivities may act as a patient's migraine triggers. Therefore, the ELISA test has potential to serve as a basis for food elimination diets to prevent chronic inflammation and onset of migraine.[6,8,9]

OBJECTIVE

The objective of this selective EBM review is to determine whether or not individualized diet restriction based on IgG against foods is effective as migraine prophylaxis in adults who suffer from migraines.

METHODS

The criteria used for the selection of the three studies included migraine sufferers without aura over 18 years old. Intervention included individualized diet restriction based on IgG antibodies, determined by ELISA. Variations existed between studies. Diet restriction based on elevated IgG to foods was compared to a "sham" diet (random elimination diet) in one randomized controlled trial or to a provocation diet (inclusion of foods with elevated IgG) in another randomized controlled trial, and to previous symptoms in one case report. Outcomes evaluated in these studies included migraine attack count and number of headache days.

Data was collected using PubMed, the Cochrane Database of Randomized Controlled Trials, and the Cochrane Databases of Systematic Reviews from 2009-2012. Key words used include “migraine prophylaxis,” “diet restriction,” “food elimination,” and “IgG.” All studies were published in peer-reviewed journals in the English language and were selected on the basis of importance of outcomes to the patient (Patient Oriented Evidence that Matters, POEMS). All studies focused on prophylaxis of migraine attacks using diet elimination based on IgG to foods. Inclusion criteria were participants over 18 years old experiencing migraine without aura; additional criteria were defined by studies (see Table 1). Exclusion criteria included outcomes that were not patient oriented and patients under 18 years old. Statistics used to evaluate patient outcomes included: p-value, CI, and IRR. The demographics and characteristics of the studies are shown in Table 1.

Table 1. Demographics & Characteristics of Included Studies

Study	Type	# Pts	Age (yrs)	Inclusion Criteria	Exclusion Criteria	W/D	Interventions
Alpay[5] (2010)	Double blind RCT	30	35±10	≥4 attacks and ≥4 headache days/month; age 18-55; treated with acute attack medications or preventative medications unchanged for 3 months; able to understand/ cooperate with study needs and diet	Suspected medication overuse; pure menstrual migraine; any other associated headache disorder	5	Individualized diet excluding specific foods with raised IgG antibodies x 6 weeks
Mitchell[6] (2011)	RCT	167	Sham diet: 47.1 ±10.1 True diet: 48.3 ±11.0	≥2 migraine like attacks or ≥4 headache days in the previous 4 week period; age 18-65; ≥1 food intolerances identified from the ELISA test (>10 AU/ml for any one food)	Any other significant co-existing pathology; no food sensitivity on the ELISA test	21	True diet (removal of intolerant foods from their diet) x 12 weeks
Nelson-Dooley[7] (2009)	Case Report	1	40	40 y.o. female with mood swings, migraines, and weight gain & PPMH of depression.	N/A	N/A	Rotation diet plan: elimination of foods with corresponding elevated IgG levels, rotated sparingly into diet; fish oil 1 cap PO BID; Women's symmetry multivitamin-mineral 1 tab PO daily; Probiotics 1 cap PO daily; glutamine 1 tsp. PO BID; free-form amino acid blend

OUTCOMES MEASURED

All outcomes measured were POEMs related to decreasing migraine frequency. Outcomes regarded as favorable in the study by Alpay and colleagues included reduction in attack count, number of headache days, number of attacks with acute medication, total medication intake, median attack severity, and mean attack duration; unfavorable outcomes were an increase in the previously mentioned values. All measures were recorded in individual headache diaries which were analyzed at baseline and at the end of each of two six week diet phases (randomized elimination and provocation diets).[6]

Mitchell and colleagues regarded a decrease in number of headache days and a lower score on the Migraine Disability Assessment Scale (MIDAS) and Headache Impact Test (HIT-6™) to be favorable outcomes. Increased values were considered unfavorable outcomes. Such values were reported by patients in a baseline questionnaire and migraine symptoms and diet adherence were recorded in a 12 week diary.[8]

In a case study, Nelson-Dooley regarded a patient-reported decrease in intensity and frequency of migraines, as well as decreased medication use during attacks as favorable outcomes.[9]

RESULTS

Three studies compared the use of elimination diets based on positive IgG antibodies against foods to prevent migraines in patients over 18 years old with a history of migraine without aura. One was a double-blind randomized controlled cross over trial,[6] one was a single blind randomized controlled trial,[8] another was a case report.[9] No intervention-related negative side effects or adverse events were reported in any of the studies.

Alpay and colleagues studied 30 patients diagnosed with migraine without aura who were recruited from a headache outpatient clinic. Patients excluded from the study included those who had suspected medication overuse, pure menstrual migraine, and any other headache disorder to maximize the results by eliminating patients that had known migraine etiologies. Each participant underwent a 6 week provocation diet followed by a 6 week elimination diet or vice versa, separated by a 2 week diet-free interval.. Diets were based on IgG antibodies against 266 food antigens detected by ELISA, and patients had an average of 24±11 food hypersensitivities. Patients recorded symptoms in individual headache diaries and the number of headache days, and migraine attack count was analyzed. A reduction in the number of headache days (10.5±4.4 at baseline to 7.5±3.7 on elimination diet; $p<0.001$, 95% CI) and number of migraine attacks (9.0± 4.4 at baseline to 6.2±3.8 on elimination diet; $p<0.001$, 95% CI) was observed.[6] However, the number needed to treat (NNT) is 34. Thus, the difficulty in completely removing approximately 24 foods (average number of food hypersensitivities) in addition to the cost of the ELISA and clinician visits needs to be considered especially because only one of every 34 patients will experience significant reduction ($\geq$ 50%) of migraine attack count.

Table 2. Analysis of Outcomes and Numbers Needed to Treat in Patients Undergoing IgG Based Diet Restriction for Migraine Prophylaxis by Alpay et al.[6]

Study Author	Number of patients	CER (%)	EER	RRI	ARR (%)	NNT
Alpay	30	20	23	1	3	34

Mitchell et al studied 167 patients recruited through advertisements and a press release with self-reported headaches that were ‘migraine like’ for at least 12 months according to their baseline questionnaire. Candidates with no identified food intolerance identified on the ELISA test were excluded in the study, as well as those who have significant co-existing pathology.

Participants underwent either a true diet (elimination of foods with elevated IgG on ELISA) or a sham diet in the control group for 12 weeks. Patients were asked to record frequency, symptoms, medication use, and clinician visits, and MIDAS and HIT-6™ at baseline, as well as all migraine qualities and diet compliance in a daily diary throughout the 12 week diet period. Patients were followed up at 4 and 12 weeks, and diaries were analyzed. At 4 weeks, the number of migraine like headaches was reduced from baseline (IRR 95% CI 1.01 to 1.50, p=0.04); however after a full 12 weeks, the difference was not statistically significant (IRR 1.15 95% CI 0.94 to 1.41, p=0.18).[8] Because the outcomes measured were not dichotomous, NNT could not be calculated.

Table 3. Analysis of Outcome of Number of Headache Days in Patients Undergoing IgG Based Diet Restriction for Migraine Prophylaxis by Mitchell et al. [8]

Time point	IRR	95% CI	p
12 weeks	1.15	0.94-1.41	0.18
4 weeks	1.23	1.01-1.50	0.04

In a case report by Nelson-Dooley, a 40-year-old female patient diagnosed with migraine and mood disorder had migraines 4-6 times per week. Plasma amino acids, urinary neurotransmitter catabolites, and serum food antibodies were obtained. The patient's enzyme immunoassay showed severe antibody reaction (+5) to casein, milk, and egg white, moderate antibody reactions (+3/+4) to 22 foods and mild antibody reactions (+1/+2) to 5 foods. The patient eliminated all foods with IgG levels of +4 and +5 for one month, and then slowly rotated them into her diet. Foods with +1 to +3 antibodies were rotated $\leq$2 times per week. This was continued for 90 days. The patient was also simultaneously prescribed various other interventions (see Table 1). Results were subjective, and reportedly the frequency of migraine attacks was "greatly reduced," and occurred only with menses versus "all the time" at baseline.

Medication use was decreased from weekly at baseline to monthly at the end of the diet. The patient did report difficulty complying with the diet, especially avoiding eggs and dairy.[9]

DISCUSSION

Specific food triggers are known to provoke migraine attacks in some individual patients, and because the triggering foods vary from patient to patient,[2] it may be related to hidden food allergy.[5,6,8] Therefore, individual diet plans to prevent migraine headaches are warranted and may be key to future therapy for this common debilitating syndrome.

However, limitations exist in obtaining evidence for expansion of the theory describing allergy mediated inflammation triggering migraine attacks. The following are limitations shared amongst all three studies. Symptoms and severity are highly dependent on the individual patient and are entirely subjective. Additionally, there may be many migraine triggers for each individual patient, which may include and are not limited to bright lights, stress, lack of sleep, missed meals, and menses.[2] It is unrealistic and nearly impossible to eliminate all of these confounding factors in order to definitely pinpoint one element as the sole migraine trigger. Regarding study designs, adhering to an elimination diet can be challenging, especially when patients have multiple food intolerances. Being conscious of ingredients, especially when dining out or eating processed foods, makes the task more daunting to strictly adhere to such a diet.

There were also specific limitations in the study design by Alpay and colleagues. Because the patients were modifying their diets at home based on the assigned diets and food was not supplied to the patients, compliance to the intervention was unknown and unmeasured. In the same study, the sample size was small (n=30), making it difficult to generalize the results to an entire population of patients diagnosed with migraine. Five patients withdrew from the

study for reasons such as “moving to another city,” “unwillingness to maintain diet,” or “skipping the visit,” and worst case analysis was not completed to account for the lost subjects. Additionally, because the author did not include a table of patient demographics, the results cannot be generalized to similar patients because the type of patients is unknown.

One of the weaknesses of the study by Mitchell and colleagues is that the participants had self-reported migraines and were not required to be clinically diagnosed with migraine by a medical provider to be included in the study. It is possible that some of the participants were suffering from other forms of headache, so the dietary manipulation would be ineffective or simply inappropriate. The daily diary was a limitation as well, as only 52% of patients on the true diet returned their completed diary so adherence is unknown in the other 48%. Additionally, because all patients were volunteers recruited through advertising, they may be more willing to comply with challenging diet modifications than the average patient.

The major drawback in the case study by Nelson-Dooley, was the simultaneous introduction of various prescriptions and interventions with the change in diet, all of which were initiated at the same time. It makes it difficult to accurately correlate the elimination diet with the patient’s reported decrease in migraine symptoms and severity. Additionally, the author did not report any measurable outcomes (eg. numerical pain scale rating); the outcomes were purely subjective and patient reported. Again, because the sample size only included one patient who also had another co-morbid diagnosis, these results cannot be generalized to an entire population.

The ELISA food panel itself is widely available and accessible at a variety of lab companies in the U.S., but the number and types of foods tested varies in each laboratory. The test is more sensitive than skin prick testing in allergy testing , is a safer choice in patients at risk for anaphylaxis or provocation of symptoms, and the single venipuncture required is easier to

tolerate. However, it is more expensive than skin prick methods. Because ELISA for food allergy is not typically indicated for patients with head pain, insurance coverage is dependent on the insurer and individual plan. Current indications for the ELISA food panel are used diagnostically for allergy mediated respiratory and gastrointestinal symptoms and diseases. There are no current contraindications or risks of the test itself.[10]

CONCLUSIONS

Some reduction of migraine frequency was demonstrated by all three studies, however the evidence is inconclusive. Because the sample size in the study by Alpay and colleagues was small and the NNT was high, results are not generalizable and may not be worthwhile for the average adult with migraines. The results shown by Mitchell and colleagues are conflicting, as a statistically significant reduction in migraine frequency was demonstrated at 4 weeks, but not at the completion of the study (12 weeks). In the case study by Nelson-Dooley[9], multiple simultaneous treatment interventions and subjective reduction in migraine frequency does not conclusively demonstrate that symptom reduction correlates with elimination diet alone.

Future study to evaluate prophylactic diet elimination based on IgG against foods for migraine frequency reduction is warranted. Larger studies with a longer intervention period ($\geq$4 weeks), with more controlled meals involving supplied meals for participants is necessary to ensure that the diet is more strictly enforced and monitored. Removal of confounding factors during the diet phase may implement the direct relationship between migraine and food allergy. Although the reviewed studies do show some promise, additional research is necessary before the use of an elimination diet for reduction of migraine frequency is recommended routinely.

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