Is there an association between migraine and allergic rhinitis?

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Abstract

We conducted a prospective study to evaluate nasal signs and symptoms and to perform allergen-specific immunoglobulin E (IgE) testing to investigate the relationship between migraine and allergic rhinitis. Our study group consisted of 40 patients diagnosed with migraine—22 men and 18 women, aged 21 to 38 years (mean: 25.7). We compared their findings with a control group of 40 healthy adults—15 men and 25 women, aged 19 to 36 years (mean: 25.1). Allergen-specific IgE measurements were obtained with six groups of allergens: fungi, grass pollens, tree pollens, wild herbs, house dust mite 1, and house dust mite 2. We found no significant difference between the migraine patients and the controls in the incidence of nasal signs and symptoms (i.e., discharge, congestion, itching, and sneezing) or inferior turbinate signs (i.e., color and edema). According to the IgE assays, 14 migraine patients (35.0%) were sensitized to one or more allergens, compared with 11 of the controls (27.5%); the difference was not statistically significant. Sensitization was highest for the grass pollens panel in both groups. Even though we did not find an association between migraine and allergic rhinitis, the recent literature supports a correlation between migraine and atopy. The two conditions share common neural pathways and common mediators, and they can be linked statistically in patients and their families. A pathophysiologic association between the two conditions seems more likely than an etiologic association. In this regard, future efforts could be focused on the determination of atopy in migraine patients and the therapeutic implications of this diagnosis.

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Introduction

Migraine is a chronic neurologic disorder characterized by episodic attacks of severe headache accompanied by autonomic and neurologic symptoms, such as nausea, sensitivity to light and noise and, in some patients, an aura involving neurologic symptoms.[1] In the United States and Western Europe, the 1-year incidence of migraine is 11% among adults: 6% among men and 15 to 18% among women.[1]

The disabilities associated with migraine can be severe. Migraine imposes considerable burdens on the patient and on society, as well.[2,3] The World Health Organization had rated severe migraine as one of the most disabling chronic disorders, along with quadriplegia, psychosis, and dementia.[2,4]

A wide range of underlying mechanisms for migraine has been postulated. Possible causes include sterile neurogenic inflammation, defects in arachidonic acid or serotonin metabolism, cyclical changes in ovarian hormone concentrations, food allergy, and atopy.[5] It has been recommended that comorbidities be considered when choosing a prophylactic agent for all these patients. Obesity, epilepsy, asthma, depression, and sleep disturbances are relatively common among this population, and they can have an influence on which agent is chosen.[1]

The possibility of a migraine-allergy link has been debated for more than a century. In 1952, Unger and Unger found a personal history of allergy in 32 of 55 migraineurs (58%).[6] They noted that these patients experienced complete relief of their migraines after complying with a diet that excluded certain trigger foods such as milk, chocolate, and wheat. They concluded that "migraine is basically an allergic disease."

As far back as the mid-1960s, Shapiro and Eisenberg studied a series of 100 patients who had been diagnosed with "allergic headache."[7] They were managed with allergy therapy, primarily immunotherapy (94%), and/or dietary restriction (17%). Based on subsequent patient interviews, they found that 36% of their patients were free of headaches, 40% were greatly improved, 19% were moderately improved, and only 5% were unchanged.

Table 1. Comparison of demographic data in the two groups

	Migraine (n = 40)	Control (n = 40)	Statistical difference
Sex, n (%)			
Male	22 (55.0)	15 (37.5)	$p = 0.116$, $\chi^2 = 2.464$
Female	18 (45.0)	25 (62.5)	
Age, yr			
Range	21 to 38	19 to 36	$p = 0.779$, $z = -0.281$
Mean ± SD	25.72 ± 4.28	25.12 ± 4.40	

Two decades later, Lehrer et al reported headache relief in 31 of 34 allergic patients (91%) on immunotherapy, with a complete resolution in 9 of them (26%).[8] All patients were described as having had "frontal" headaches without further classification, but typical migraine symptoms (e.g., aura, throbbing, and nausea) were not reported in this patient population.

Kemper at al performed a meta-analysis of literature published on migraine and immune system function and found evidence to support an elevation of immunoglobulin E (IgE) levels in patients with atopic migraine, but not in migraine patients without type I hypersensitivity.[9] Their findings also suggested a higher histamine plasma level in patients with migraine (atopic or otherwise) and an increase in levels of plasma tumor necrosis factor alpha (TNF-α).

In this article, we describe our study of the relationship between migraine and allergy.

Patients and methods

We conducted a prospective study of 40 patients—22 men and 18 women, aged 21 to 38 years (mean: 25.7)—who were diagnosed with migraine headache in the Department of Neurology at the Eskişehir Osmangazi University Faculty of Medicine. The diagnosis was based on International Headache Society (IHS) criteria:

- at least five headache attacks lasting 4 to 72 hours at a time;
- headaches with at least two of the following characteristics: unilateral location, pulsating quality, moderate to severe intensity manifested by inhibition or prohibition of daily activities, and aggravation by walking stairs or engaging in similar routine physical activities;
- at least one of the following symptoms during an attack: nausea, vomiting, phonophobia, and photophobia;
- headache that was not attributed to another disorder, including stroke, cerebral palsy, trigeminal neuralgia, seizure disorder, or acute or chronic sinusitis.[10,11]

For comparison purposes, we recruited a control group of 40 healthy volunteers—15 men and 25 women, aged 19 to 36 years (mean: 25.1)—who were affiliated with the same hospital. There were no statistically significant differences between the controls and the migraine group in terms of sex ($p = 0.116$) and age ($p = 0.779$) (table 1).

Nasal signs and symptoms. We used a questionnaire to quantify the presence of nasal signs and symptoms (i.e., discharge, congestion, itching, and sneezing) and inferior turbinate signs (i.e., color and edema). Turbinate color was rated on a 4-point scale as *natural* (0 points), *pale* (1), *bluish* (2), and *severely pale or bluish* (3), and turbinate signs was rated as *present* or *absent*.

Allergen-specific IgE levels. We obtained blood samples from all participants to measure their allergen-specific IgE level against six groups of allergens: fungi, grass pollens, tree pollens, wild herbs, house dust mite 1, house dust mite 2. Participants were considered to be sensitized if their radioallergosorbent test (RAST) rating was 2 or higher (i.e., ≥0.7 kU/L); a RAST rating of 3 or higher (>3.50 kU/L) is considered highly sensitized, and a rating of 0 or 1 (<0.7 kU/L) is considered negative.

Degree of atopy was based on the number of allergens to which a patient was sensitive. Participants were considered to have a high degree of atopy if they were sensitized to three or more groups of allergens.

Finally, we evaluated whether the rhinitis was seasonal, perennial, or both.

Statistical analysis. Statistical analysis was performed with the Statistical Package for the Social Sciences software for Windows (v. 16.0). Comparisons were made with the Mann-Whitney *U* test, chi-square (χ^2) test, and Spearman correlation rho efficient test. A p value <0.05 was considered to be statistically significant.

Ethical considerations. This study was conducted in accordance with the Declaration of Helsinki.[12] All participants provided signed informed consent. Local Ethics Board approval was granted by the Eskişehir Osmangazi University Faculty of Medicine.

Table 2. Comparison of specific IgE sensitivity to allergens in the two groups

	Migraine (n = 40)			Control (n = 40)			
Allergen	**Mean ± SD**	**Min**	**Max**	**Mean ± SD**	**Min**	**Max**	**Statistical difference**
Fungi	0.12 ± 0.51	0	3	0.17 ± 0.67	0	3	$p = 0.975$, $z = -0.032$
Grass pollens	0.77 ± 1.22	0	4	0.70 ± 1.39	0	4	$p = 0.504$, $z = -0.667$
Tree pollens	0.22 ± 0.53	0	2	0.17 ± 0.50	0	2	$p = 0.556$, $z = -0.589$
Wild herbs	0.27 ± 0.59	0	2	0.22 ± 0.57	0	2	$p = 0.590$, $z = -0.538$
House dust mite 1	0.45 ± 0.93	0	3	0.37 ± 0.83	0	3	$p = 0.757$, $z = -0.310$
House dust mite 2	0.45 ± 0.93	0	3	0.50 ± 1.01	0	3	$p = 0.937$, $z = -0.079$

Results

Nasal signs and symptoms. There were virtually no differences between the migraineurs and the controls in nasal signs and symptoms and turbinate signs.

Discharge was present in 95.0% of the migraineurs and 92.5% of the controls, respectively ($p = 0.804$, $\chi^2 = 0.989$). Nasal congestion was also present in 95.0 and 92.5%, respectively ($p = 0.882$, $\chi^2 = 0.022$). Itching was reported by 100 and 97.5% ($p = 0.448$, $\chi^2 = 2.656$) and sneezing by 100 and 97.5% ($p = 0.207$, $\chi^2 = 1.592$).

The inferior turbinate was pale, bluish, or severely pale or bluish in 95.0% of the migraine group and in 97.5 of the control group ($p = 0.220$, $\chi^2 = 4.420$). Inferior turbinate edema was present in 80.0 and 77.5% of the two groups, respectively ($p = 0.928$, $\chi^2 = 0.150$).

Allergen-specific IgE results. Of the 40 migraine patients, allergen-specific IgE measurements revealed that 14 (35.0%) were sensitized to at least one group of allergens. By comparison, 11 of the 40 controls (27.5%) were sensitized. The overall difference between the two groups was not statistically significant, nor were any of the differences with respect to the six individual types of allergen (table 2).

Of the 14 sensitized migraineurs, 6 (42.9%) were highly sensitized (RAST rating: ≥3), which indicated a high degree of atopy. Seven of the 11 controls (63.6%) were highly sensitized. Again, the difference was not significant (table 3).

Finally, there was no statistically significant difference between the two groups as to whether the rhinitis was seasonal, perennial, or both (table 3).

Discussion

The association between migraine headache and atopic diseases that has been found in previous epidemiologic studies led researchers to look for evidence of immune system dysfunction in migraineurs. Changes in serum levels of complement, immunoglobulins, histamine, cytokines, and immune cells were found in some of these studies.[9] In 1985, Nelson, in his lecture on atopic diseases, named migraine among the atopic diseases such as eczema, asthma, and rhinitis that comprise a group of seemingly unrelated conditions that cluster in individuals and families.[13]

An epidemiologic study by Derebery et al on rhinitis and comorbidities in the United States found that the incidence of migraine was significantly higher in patients with rhinitis than in those without rhinitis (17.3 vs. 7.6%).[14] A study by Ku et al found a significantly higher incidence of migraine in patients with allergic rhinitis than in those without it (34 vs. 4%).[15]

Likewise, in a study from Iran, Saberi et al found that migraine was significantly more common in allergic rhinitis patients than in those with no history of allergic rhinitis (37 vs. 5%).[16] Most of those migraines occurred without aura. The incidence of migraine without aura was significantly higher in the allergic rhinitis patients than in the controls, but there was no significant difference between the two groups in the incidence of migraine with aura. This finding may be important in the context of our findings.

In our study, we wondered if the prevalence of allergic rhinitis would be higher in migraine patients than in controls. It was not. RAST results showed that the incidence of atopic sensitization was not significantly higher in the migraine patients than in the controls (35.0 vs. 27.5%). We also failed to find any significant difference between the two groups in sensitization to specific allergens, degree of atopy, or seasonality. However, it should be kept in mind that RAST is not as

Table 3. Sensitivity to allergens, degree of atopy, and seasonality of rhinitis in specific IgE-positive patients

	n (%)	
	Migraine (n = 14)	**Control (n = 11)**
Allergen		
Fungi	1 (7.1)	2 (18.2)
Grass pollens	11 (78.6)	8 (72.7)
Tree pollens	2 (14.3)	2 (18.2)
Wild herbs	3 (21.4)	3 (27.3)
House dust mite 1	6 (42.9)	5 (45.5)
House dust mite 2	6 (42.9)	7 (63.6)
Degree of atopy		
Low (<3 allergens)	8 (57.1)	4 (36.4)
High (≥3 allergens)	6 (42.9)	7 (63.6)
Seasonality of rhinitis		
Perennial	2 (14.3)	2 (18.2)
Seasonal	7 (50.0)	4 (36.4)
Both	5 (35.7)	5 (45.5)

accurate as ImmunoCAP and skin testing in diagnosing allergic rhinitis.[17-19]

Although previous studies comparing patients with allergic rhinitis and controls found a higher rate of migraine in the former and our study did not, the explanation for the difference may lie in the definition of migraine, specifically migraine without aura. It is possible that the current classification of migraine without aura has resulted in more patients with allergic rhinitis and/or sinus headache being defined as migraineurs and thus being given migraine treatment. Moreover, owing to the common pathophysiology of these diseases, migraine treatment can be successful in these group of patients, as well.

It is also important to mention that there is a high prevalence of allergic rhinitis in the Central Anatolia region of Turkey, where our study was undertaken. The overall rate of allergic rhinitis in this region as evaluated by the Score for Allergic Rhinitis study was 28.7%; this rate might be even higher in the urban areas.[20] Therefore, given the relatively small number of cases in our study, the high rate of atopy here might have skewed our findings and masked a possible association between migraine and allergic rhinitis.

Not only did our study fail to find a relationship between atopy and migraine, we found no significant difference in allergic signs and symptoms, such as nasal discharge, nasal congestion, and turbinate edema. These signs and symptoms can trigger sinus headaches.

Conversely, other studies of the incidence of migraine diagnosis among sinus headache patients who were referred to otolaryngologists have found a strong relationship. Mehle reported that well over 50% of sinus headache patients satisfied the IHS criteria for migraine headache.[21] In a tertiary care otolaryngology practice, Perry et al reported that 58% of patients with a chief complaint of sinus headache despite normal physical examination findings and negative computed tomography scans were diagnosed with migraine.[22]

In 2002, Cady and Schreiber reported that a detailed history obtained from 47 patients with self-described sinus headache revealed that 98% of these patients experienced headaches with symptoms that met the IHS criteria for migraine (70%) or migrainous (28%) headache (i.e., probable migraine).[23] In a large study, Schreiber et al found that 80% of 2,991 "sinus headache" patients met the IHS criteria for migraine and another 8% had migranous headache.[24]

In the Sinus, Allergy and Migraine Study, Eross et al found that 86 of 100 consecutively presenting self-diagnosed sinus headache patients actually had migraine or probable migraine.[25] Only 3% of them had rhinosinusitis-attributable headache. The common migraine triggers in these patients included weather changes (83%), seasonal variations (73%), exposure to allergens (62%), and changes in altitude (38%).

Thus, there is ample evidence of some association among migraine, sinus headache, and allergy. Whether this relationship is attributable to a common pathophysiology or a common etiology is still a matter of debate, but we believe that a pathophysiologic association is more likely.

The current neurovascular model describes the migraine process as starting in the brain, with subsequent sensitization of the peripheral trigeminal neurons, including those that supply sensation of the meninges.[26] The predominantly peripheral early phase of trigeminal nerve sensitization may lead to central sensitization at the level of the trigeminal nucleus caudalis in the brainstem and pain in the distribution of the ophthalmic and/or maxillary divisions of the trigeminal nerve.[21] Pain arising in these fibers may result in secondary parasympathetic nasal signs and symptoms similar to the signs and symptoms of allergic rhinitis.

In 2004, Cady and Schreiber reported the presence of nasal congestion and rhinorrhea during a migraine attack, based on objective endoscopic evidence.[27] They added that both allergic rhinitis and migrainous midfacial or nasal pain may be accompanied by the release of a variety of neuropeptides such as histamine, substance P, calcitonin gene-related peptide, vasoactive

intestinal peptide, nitric oxide, TNF-α, and others. In a way, migraine and allergic rhinitis share common neural pathways and immune mediators.

Other research has found that asthma is more common in patients with hay fever than in those without it.[5,28] This finding suggests that there is a link between migraine (vascular reactivity) and asthma (bronchial reactivity) that is independent of allergic mechanisms. This link might be attributable to a shared functional abnormality of smooth muscle in both blood vessels and airways.

While the literature supports a correlation between migraine and atopy, only a few clinical studies tried to assess the therapeutic implications of this association. In 1990, Mansfield discussed the role of antihistamine therapy in migraine and observed no documented benefit from H_1 or H_2 blockers in preventing migraine headaches.[29] In an open-label trial, cinnarizine, a dihydropyridine-type calcium channel blocker with antihistaminic properties, showed promise in migraine prophylaxis.[30] Research on antagonists/inverse agonists of the H_3 receptor is progressing in clinical trials, and these agents might find their application in the treatment of migraine or allergic rhinitis.[31]

In 2002, de Souza Carvalho et al studied 6 children and adolescents with asthma and migraine and noted that treatment with montelukast at 5 mg daily for 24 weeks lowered the number of reported asthma attacks and significantly decreased the frequency of headaches compared with baseline.[32] However, other studies failed to confirm those results.[33,34]

Two other promising studies on immunotherapy for migraine were published in 2011. The first, by Theodoropoulos et al, involved 7 patients with migraine and allergic rhinitis who were treated with sublingual immunotherapy.[35] Diagnosed allergies included dust mites, weeds, tree pollen, grasses, various molds, and animal dander. The success of therapy was monitored with measurements of interictal serum C-reactive protein (CRP) levels. The investigators noted a clear reduction in CRP levels over a period of 10 to 12 months in 4 of the 7 patients. In addition, the overall reduction in CRP for all 7 patients was clinically significant compared with controls. The response of migraines to the treatment of allergy suggests that there is an allergic component to the mechanism of migraines.

The second study, by Martin et al, looked at migraine headache in 536 patients with allergic rhinitis and an established allergic sensitization to airborne allergens.[36] The overall incidence of migraine was 32.5%; it was not associated with the degree of allergic sensitization. A higher frequency of migraine was observed with increasing percentages of positive allergy tests in a high-atopy group, which suggested the presence of a threshold above which greater degrees of atopy could provoke a migraine headache. We were unable to identify such a difference in our study.

In the study by Martin et al, immunotherapy administered to patients aged 45 years and younger resulted in a 52% reduction in the frequency of migraine headache and a 45% reduction in related disability.[36] These findings suggest that the degree of allergic sensitization was more modulatory for migraine (e.g., influencing frequency and disability) than causative (e.g., modulating the presence or absence of migraine).

The possible link between migraine and perennial allergies can also be explained by a causal relationship. Long-lasting nasal signs and symptoms in perennial allergies may have an additive effect on inflammation-induced trigeminal hyperalgesia and result in increased migraine vulnerability. Therefore, the duration of signs and symptoms of allergic rhinitis might have an effect on the development, frequency, and severity of migraine headache. Future clinical studies could focus on these mechanisms.

An association between migraine and atopic diseases was found in the epidemiologic study by Ku et al.[15] They reported that a diagnosis of migraine in rhinitis patients with headache was 14.3 times more common in atopic patients than in nonatopic patients. However, in our controlled study, allergen-specific IgE measurements did not find any statistically significant difference in the rate of allergic rhinitis between migraine patients and a healthy population. Moreover, there was no significant difference in the incidence of allergic signs and symptoms such as nasal discharge, nasal congestion, and inferior turbinate edema between the two groups. These signs and symptoms might serve as triggers of sinus headaches as well as migraine attacks.

Previously reported data have supported the idea that migraine patients with allergy sensitization may benefit from therapies directed to allergy. Whatever the reason, we believe that a pathophysiologic association between migraine and allergic rhinitis is more likely than an etiologic association. In this regard, investigation and identification of allergic rhinitis in patients with a diagnosis of migraine could be useful in the management of migraine.

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