

Allergens might trigger migraine attacks

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Abstract Migraine is a common primary headache disorder. The mechanisms underlying the onset of a migraine attack are not completely understood. Environmental changes and a number of other factors could induce migraine attacks. The aim of this study was to investigate the relationship between the frequency of migraine attacks and allergens. Migraine patients without aura, and healthy individuals similar in age and gender without a history of headache and allergy were prospectively included in the study. The duration of migraine, the frequency of migraine attacks, the medication history, and the symptoms during attacks were questioned. Migraine disability assessment score (MIDAS) and visual analog scale (VAS) scores were obtained. Allergen extracts including dust, fungi, insect, animal epithelium, pollens, and food allergens were applied for allergy tests. 49 migraine patients and 49 healthy individuals were enrolled in the study. There was no significant difference in terms of age and gender. The median migraine disease duration, the number of attacks in a month, and the duration of attacks were, respectively, 5.5 years (1–44), 4 (1–10) day/month, and 24 (4–72) h. The mean MIDAS grade was 2.45 ± 0.14 (1–4), and mean VAS score was 7.89 ± 0.27 (4–10). The positivity of allergy tests was 55.1 % (27/49) in the migraine group and 32.7 % (16/49) in the control group ($p < 0.05$). The allergy

tests were positive for house dust, red birch, hazel tree, olive tree, nettle, and wheat. The frequency of migraine attacks was higher in allergy-test-positive patients than in negative ones in the migraine group ($p = 0.001$). The migraine patients who had frequent attacks should be examined for allergies.

Keywords Migraine · Allergy · MIDAS

Introduction

Migraine headache is one of the most common pain syndromes, affecting approximately 15 % of the population [1]. Although mechanisms underlying the onset of a migraine attack are not completely understood, activation of pain fibers that innervate the dura mater is believed to play a key role in promoting the intracranial pain of migraine [2]. It was shown that environmental changes and a number of other factors—such as diet, stress, smoking, and exercise—could induce migraine attacks [3].

The opinion regarding the relationship between migraine and allergy has been discussed for many years [1]. Several epidemiologic and clinic-based studies have demonstrated an association between migraine, asthma, and allergy. In a case-control study with 64,678 migraine patients, the relative risk for allergy was reported at 1.59 [4]. Mansfield et al. found that 16/40 migraineurs had positive skin prick tests for food allergens, and 11 of these 16 patients had at least a 66 % decrease in headache frequency compared with baseline when they avoided the identified foods [5]. In this study, our aim was to evaluate the relationship between migraine and allergens.

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Methods

Migraine patients without aura diagnosed according to the criteria of the International Classification of Headache Disorders, 2nd edition [6], and healthy individuals similar in age and gender without a history of headache and allergy were prospectively included in the study. Patients with a history of allergy and chronic systemic illness who used H2 receptor blockers and antiallergic medications were excluded. Antidepressant drugs were discontinued at least 1 week prior to the allergy tests. The duration and frequency of migraines, the medication history, and the symptoms during attacks were questioned. Those suffering from headache disorders completed the migraine disability assessment score (MIDAS) questionnaire, which assessed the number of days in a three-month period with headache-related disability [7, 8], and visual analog scale (VAS) scores were obtained [9].

Allergy tests were performed on the migraine and control groups at an ear, nose, and throat (ENT) clinic. Allergen extracts—such as dust, fungi, insects, animal epithelium, pollens, and food allergens—were applied for allergy tests. Alyostal ST-IR (Stallegenes, SA, France) standard allergen extracts were used for skin prick testing. After cleaning the ventral side of the forearm with alcohol, a quick test applicator, which consisted of eight separate tips with the standard dose of allergen extracts, was applied to the skin. The results were evaluated 15 min later. Histamine hydrochloride was used as a positive control and isotonic NaCl was used as a negative control. As a positive control, the validity of the test criteria was greater than 3 mm and, as a negative control, less than 3 mm. If the induration diameter was observed as ≥ 3 mm, it was considered that a skin reaction to the allergen was a positive response [10]. Thirty allergen extracts common for a skin prick test; negative controls, and positive controls were applied to the forearm skin with four applicators. Allergen extracts included: 2 h (d. farinae, d. pteranissinu), three fungi (alternaria, aspergillus, cladosporium), one insect (cockroach), three animal epithelium (catfur, dog fur, and poultry), 15 pollens (red birch, hazel tree, lime tree, sycamore tree, maple tree, poplar tree, willow tree, pine tree, olive tree, cereals (mixed barley, wheat, corn, oats, and wheat pollen), bright, crazy, meadow bunch grass, gold spike, black tie turkey, chamomile herb, vernal, daisy grass, stinging nettle grass), and six food allergens (fish, egg whites, egg yolks, nuts, orange, and strawberry).

Statistical analysis

The Shapiro–Wilks test was used to determine the continuous variables with a normal distribution. Mean and

standard deviation (mean $\pm$ SD) values were provided for variables with a normal distribution. The number (n) and percent (%) values were given for categorical variables. The χ^2 or Fisher exact test was used to compare group data for categorical variables.

All statistical analyses were performed with the IBM SPSS Statistics 21.0 (IBM Corp. Released 2012. IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp.) and MS-Excel 2007 software programs. The statistical significance level was set at $p < 0.05$.

Results

There were 49 patients with migraine and 49 healthy individuals enrolled in the study. The demographic variables and clinical characteristics were similar between the two groups. There was no significant difference between a mean age of 38.38 ± 8.30 years (range 24–60 years) vs. 36.93 ± 9.52 years (range 23–59) ($p = 0.42$) in patients with migraine compared to the control group. The median duration of migraine disease, the number of attacks in a month, and the duration of the attacks were, respectively, 5.5 years (1–44), 4 (1–10) day/month, and 24 (4–72) h. Mean MIDAS grade was 2.45 ± 0.14 (1–4) and VAS score was 7.89 ± 0.27 (4–10).

Symptoms included nausea in 95.7 % of the patients, phonophobia in 91.3 % of the patients, photophobia in 80.4 % of the patients, and vomiting in 58.7 % of the patients. Twenty-three percent of migraine patients used analgesics and 76.1 % received triptans during attacks. Of the 49 patients, 22 (44.8 %) were using preventive medications. The demographic features of the migraine patients, the parameters of headache, and the medications are listed in Table 1.

The positivity of allergy tests was 55.1 % (27/49) in the migraine group and 32.7 % (16/49) in the control group ($p < 0.05$). Allergy tests for d. pteranissinu, red birch, hazel tree, olive tree, wheat pollen, and stinging nettle grass were significantly higher in patients in the migraine group compared to those in the control groups (55.6 vs. 4.5 %, $p = 0.000$; 29.6 vs. 4.5 %, $p = 0.026$; 18.5 vs. 0 %, $p = 0.042$; 25.9 vs. 0 %, $p = 0.010$; and 40.7 vs. 4.5 %, $p = 0.013$, respectively), as shown in Table 2.

The median frequency of migraine attacks (day/month) was significantly higher in patients with allergy-test-positive migraines than in patients with allergy-test-negative migraines [4 (2–10) vs. 3 (1–10), $p = 0.001$]. There were no significant differences for mean age (years) (38.48 ± 7.23 vs. 38.27 ± 9.63 , $p = 0.931$), female gender (88.9 vs. 77.3 %, $p = 0.171$), MIDAS grades of 3 and 4 (50 vs. 35 %, $p = 0.144$), VAS scores of 9 and 10 (50 vs.

Table 1 The demographic features of migraine patients

Age (mean $\pm$ SD)	38.38 $\pm$ 8.30 (24–60)
Gender	
Female	41 (83.7 %)
Male	8 (16.3 %)
Duration of migraine/year (mean $\pm$ SD)	7.23 $\pm$ 1.21
Frequency of attacks day/month (mean $\pm$ SD)	4.19 $\pm$ 0.35
Duration of attacks/hour (mean $\pm$ SD)	40.43 $\pm$ 3.34
Symptoms (%)	
Nausea	95.7
Phonophobia	91.3
Photophobia	80.4
Vomiting	58.7
MIDAS grade (mean $\pm$ SD)	2.45 $\pm$ 0.14 (1–4)
MIDAS score >2	20 (%40.8)
VAS (mean $\pm$ SD)	7.89 $\pm$ 0.27 (4–10)
VAS >8	20 (%40.8)
Attack treatment (%)	
Analgesics	23.9
Triptans	76.1
Prophylaxis	22 (44.8 %)
Beta-blockers	8 (36.3 %)
Calcium channel blockers	4 (18.2 %)
Antiepileptics	10 (45.5 %)

35 %, $p = 0.144$), median duration of migraine disease (year) [6 (1–30) vs. 3.5 (1–44), $p = 0.433$], or median duration of attacks (hour) [48 (4–72) vs. 24 (6–72), $p = 0.344$] in migraine patients with allergy test positive compared to allergy test negative. Twenty-seven allergy-test-positive patients had MIDAS grades above 3 and VAS scores above 9, but these were not significant compared to the migraine sufferers without allergy ($p = 0.144$), as shown in Table 3.

Discussion

Intracranial headaches, such as migraines, are generally accepted to be mediated by prolonged activation of meningeal nociceptors. However, the mechanisms responsible for such nociceptor activation are poorly understood [2]. The dura mater is the one intracranial structure most heavily innervated by pain fibers, but it is also densely populated by immune cells, including resident mast cells (MC), and granulated immune cells that play a critical role in inflammation. MC reside in close proximity to trigeminal afferents located in the dura of both humans and rodents [11].

Allergens could activate trigeminal afferents through the enhanced release of inflammatory mediators from dural mast cells [2]. Previous studies have shown that electrical

stimulation of the trigeminal nerve, a model of intracranial pain, evokes degranulation of dural MC—a process likely to contribute to local meningeal inflammation [12]. It was considered that vasodilator substances and cytokines released from mast cells may play a role in the vasodilator phase of migraine and meningeal inflammation [1].

In 1979, Grant et al. reported the relationship between food allergy and migraine. Migraine was then classified in the atopic diseases group [13]. In another study, Sillanpaa et al. reported that 39.5 % of boys and 46.2 % of girls (between 7 and 22 years of age) with migraine headaches reported allergy symptoms [14]. In 2006, Artto et al. studied 1000 migraine family members and found that 25.4 % of men and 37.4 % of women with migraine headache reported a history of atopy, and familial migraine was found to be comorbid with allergy [15]. Ku et al. conversely studied the incidence of migraine in allergy sufferers and found that patients with symptoms of allergic rhinitis were significantly more likely to satisfy migraine criteria [16]. It was reported that IgE-mediated mechanism and histamine might play a role in the relationship between allergy and migraine [1].

Eross et al. found that many migraine or probable migraine patients reported headache triggers, such as weather changes (83 %), seasonal variation (73 %), and exposure to allergens (62 %). Allergens reported as triggers included grass, trees, dust, foods, animal danders, and

Table 2 The comparisons of allergen types in migraine and control groups

Allergens	Allergen type	Migraine group, % (n)	Control group, % (n)	p
House dust	D. farina	14.8 (4)	0 (0)	0.83
	D. pteranissinu	55.6 (15)	4.5 (1)	0.000
Pollens (tree)	Red birch, hazel tree	29.6 (8)	4.5 (1)	0.026
	Lime tree, sycamore tree, maple tree	11.1 (3)	4.5 (1)	0.387
	Poplar tree	14.8 (4)	4.5 (1)	0.245
	Willow tree	11.1 (3)	0 (0)	0.159
	Pine tree	14.8 (4)	0 (0)	0.083
	Olive tree	18.5 (5)	0 (0)	0.042
	Mixed barley, wheat, corn, oat	22.6 (6)	4.5 (1)	0.08
Pollens (cereals)	Corn pollen	11.1 (3)	0 (0)	0.16
	Wheat pollen	25.9 (7)	0 (0)	0.01
	Bright, crazy, meadow bunch grass	22.2 (6)	4.5 (1)	0.086
Pollens (grass)	Gold spike, black tie turkey, chamomile herb	3.7 (1)	1 (1)	0.702
	Vernal	18.5 (5)	4.5 (1)	0.148
	Daisy grass	18.5 (5)	4.5 (1)	0.148
	Stinging nettle grass	40.7 (11)	4.5 (1)	0.013
	Cat fur	3.7 (1)	0 (0)	0.551
Animals	Dog fur	7.2 (2)	0 (0)	0.298
	Cockroach	22.6 (6)	4.5 (1)	0.086
Food	Fish	1.1 (3)	4.5 (1)	0.371
	Egg whites	3.7 (1)	4.5 (1)	0.702
	Egg yolks	3.7 (1)	4.5 (1)	0.702
	Nuts	7.4 (2)	4.5 (1)	0.578
	Orange	7.4 (2)	4.5 (1)	0.578
	Strawberry	3.7 (1)	4.5 (1)	0.702
	Alternaria	7.4 (2)	0 (0)	0.298
Fungi	Aspergillus	3.7 (1)	0 (0)	0.551
	Cladosporium	3.7 (1)	0 (0)	0.551

Table 3 The comparison of allergy test positive and negative migraine patients

	Allergy test (+) n: 27	Allergy test (–) n: 22	p
Mean age	38.48 ± 7.23	38.27 ± 9.63	0.931
Gender (female) (n: 41)	88.9 %	77.3 %	0.171
MIDAS grade 3 and 4 (n: 20)	50 %	35 %	0.144
VAS score 9 and 10	50 %	35 %	0.144
Duration of migraine/year (median/min–max)	6 (1–30)	3.5 (1–44)	0.433
Frequency of attacks day/month (median/min–max)	4 (2–10)	3 (1–10)	0.001
Duration of attacks/hour (median/min–max)	48 (4–72)	24 (6–72)	0.344

mold [17]. Grant presented 60 patients with migraine who were treated with elimination diets and became headache-free. The foods most commonly associated with migraine were wheat, orange, eggs, tea, coffee, chocolate, milk, beef, corn, cane sugar, and yeast [18]. Some studies support the relationship between migraine and atopy. Both of these diseases use the same mediators and neural pathways,

but the exact relation between these diseases is not clear [19].

In this study, allergy tests were positive in 27 of 49 (55.1 %) migraine patients and in 16 of 49 (32.7 %) control-group patients. Positivity of allergy was found to be associated with the frequency of migraine attacks, but there was no association with the severity of the attacks. This could suggest

that allergy is more modulatory for migraine frequency. Our investigation showed that migraine patients were allergic to d. pteranissinu, red birch, hazel tree, olive tree, wheat pollen, and stinging nettle grass. This might explain the regional and international variations of migraine prevalence. In Turkey, the prevalence of migraine was 11.4–14.7 % in the Marmara, Black Sea, Aegean, Mediterranean, and Central Anatolia regions. Red birch, hazel tree, olive tree, wheat pollen, and stinging nettle grass are mostly grown in this area. The greater number of allergens could provoke an allergic response, which might increase the frequency of migraine attacks.

In conclusion, many medications are used in migraine prevention, but none of these were developed specifically for migraine. There are various reasons for the failure of preventive treatment. These include: unrealistic expectations of the patient, poor drug adherence, and the overuse of abortive medication. When deciding on preventive treatment, we should keep in mind the frequency, severity, and disability of migraines, and the comorbidity with allergy. If patients with migraine have more frequent attacks despite preventive agents, neurologists should evaluate the comorbidity with migraine and allergy.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical standard The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008. Ethical approval of the study was granted by the Ethics Committee.

Informed consent Informed consent was obtained from all participants included in the study.

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