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Research Submission

Allergy and Immunotherapy: Are They Related to Migraine Headache?

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Introduction.—Several studies have reported that migraine headaches are more common in patients with allergic rhinitis and that immunotherapy decreases the frequency of headache in atopic headache sufferers.

Objective.—To determine if the degree of allergic sensitization and the administration of immunotherapy are associated with the prevalence, frequency, and disability of migraine headache in patients with allergic rhinitis.

Methods.—Consecutive patients between the ages of 18-65 presenting to an allergy practice that received a diagnosis of an allergic rhinitis subtype (eg, allergic or mixed rhinitis) were enrolled in this study. All participants underwent allergy testing as well as a structured verbal headache diagnostic interview to ascertain the clinical characteristics of each headache type. Those reporting headaches were later assigned a headache diagnosis by a headache specialist blinded to the rhinitis diagnosis based on 2004 International Classification Headache Disorders-2 (ICHD-2) diagnostic criteria. Migraine prevalence was defined as the percentage of patients with a diagnosis of migraine headache (ICHD-2 diagnoses 1.1-1.5). Migraine frequency represented the number of days per month with migraine headache self-reported during the headache interview and migraine disability was the number of days with disability obtained from the Migraine Disability Assessment questionnaire. Generalized linear models were used to analyze the migraine prevalence, frequency, and disability with the degree of allergic sensitization (percentage of positive allergy tests) and administration of immunotherapy as covariates. Patients were categorized into high (> 45% positive

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allergy tests) and low (≤45% positive allergy tests) atopic groups based on the number of allergy tests that were positive for the frequency and disability analyses.

Results.—A total of 536 patients (60% female, mean age 40.9 years) participated in the study. The prevalence of migraine was not associated with the degree of allergic sensitization, but there was a significant age/immunotherapy interaction ($P < .02$). Migraine headaches were less prevalent in the immunotherapy group than the nonimmunotherapy at ages <40 years and more prevalent in the immunotherapy group at ages ≥40 years of age. In subjects ≤45 years of age, increasing percentages of allergic sensitization were associated with a decreased frequency and disability of migraine headache in the low atopic group (risk ratios [RRs] of 0.80 [95% CI; 0.65, 0.99] and 0.81[95% CI; 0.68, 0.97]) while increasing percentages were associated with an increased frequency (not disability) in the high atopic group (RR = 1.60; [95% CI; 1.11, 2.29]). In subjects ≤45 years of age, immunotherapy was associated with decreased migraine frequency and disability (RRs of 0.48 [95% CI; 0.28, 0.83] and 0.55 [95% CI; 0.35, 0.87]). In those >45 years of age, there was no effect of degree of allergic sensitization or immunotherapy on the frequency and disability of migraine headache.

Conclusions.—Our study suggests that the association of allergy with migraine headaches depends upon age, degree of allergic sensitization, administration of immunotherapy, and the type of headache outcome measure that are studied. Lower "degrees of atopy" are associated with less frequent and disabling migraine headaches in younger subjects while higher degrees were associated with more frequent migraines. The administration of immunotherapy is associated with a decreased prevalence, frequency, and disability of migraine headache in younger subjects.

Key words: allergy, atopy, migraine headache, immunotherapy, desensitization, prevalence

Abbreviations: ICHD International Classification Headache Disorder, MIDAS Migraine Disability Assessment, RR risk ratio

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Migraine headache and allergic rhinitis are both common disorders occurring within 12.6% and 9-18% of the United States population, respectively.[1-3] Previous studies[4-6] have reported an increased prevalence of migraine headache in patients with a diagnosis of allergic rhinitis and in those experiencing symptoms of hay fever. Interestingly, the health care costs associated with the treatment of migraine headache are higher during allergy seasons than during other times of the year.[7] These data indicate that allergic rhinitis modulates the prevalence of migraine headache and its health care expenditures.

Atopy, which is the genetic predisposition to develop IgE antibodies to specific allergens, may be associated with the frequency of migraine headaches. Mansfield et al[8] 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 with avoidance of the identified foods. Seven of the skin prick positive patients later underwent double-blind placebo-controlled food challenges and 5 experienced attacks of migraine upon exposure to the previously identified food allergen. None of the 4 patients challenged with placebo experienced a migraine attack. Two other studies[9,10] found that migraine headaches improved or were eliminated altogether in patients that followed an elimination diet of common food allergens. Thus, limited data exist to support the contention that exposure to food allergens increases the frequency of migraine attacks in atopic migraineurs.

Immunotherapy (eg, allergy injections) can induce tolerance to specific allergens by altering cytokine responses of T-helper cells and through induction of IgG and IgA antibodies that block the binding of IgE to mast cells.[11] Several case series[12-14] have reported a decreased frequency of headache attacks after institution of immunotherapy in atopic headache sufferers. Many of these studies, however, were conducted prior to the publication of International Classification Headache Disorder-1 (ICHD-1) criteria for the diagnosis of headache disorders and consequently it is unknown whether these results apply to migraine, tension-type headache or other headache disorders.

The objective of this study was to characterize the relationship between migraine headache and allergic rhinitis using a large database generated as part of the Migraine, Allergy and Rhinitis Study (MARS). We hypothesized that individuals with allergic rhinitis with greater degrees of allergic sensitization (percent positive allergy tests) would be more likely to experience migraine headaches and that their attacks

would be more frequent and disabling than those with lower degrees of atopy. Therefore, the primary objective of this study was to determine if the degree of allergic sensitization and/or the administration of immunotherapy were associated with the prevalence of migraine headache in individuals with allergic rhinitis. A secondary objective was to ascertain whether these variables impacted the frequency and disability of migraine headache.

METHODS

The study was conducted at the University of Cincinnati College of Medicine and study participants were recruited from the Bernstein Allergy Group at three separate practice sites. Consecutive patients presenting to this allergy practice for an office visit were eligible for inclusion in the study. Inclusion criteria included: (1) ages 18-65 years; (2) ability to give informed consent; (3) a confirmed diagnosis of allergic or mixed (allergic rhinitis with nonallergic triggers) rhinitis. A diagnosis of allergic rhinitis required one or more positive allergy skin prick tests (wheal ≥ 3 mm compared with saline control with surrounding erythema or a class II or greater result with Immuocap analysis) that correlated with symptoms upon exposure to the relevant allergen(s). Exclusion criteria included: (1) past history of secondary headache disorders such as a brain aneurysm or brain tumor; (2) referred specifically to determine if rhinitis or allergies were responsible for their complaint of "headache"; (3) significant chronic medical illnesses such as malignancy, chronic renal failure, tuberculosis, lupus, rheumatoid arthritis, sarcoidosis, hypereosinophilic syndrome, Wegener's granulomatosis, Churg-Strauss vasculitis, and polyarteritis nodosum; (4) pregnancy. The study received approval from the University of Cincinnati Institutional Review Board and informed consent was obtained from all study subjects.

All participants were asked if they had experienced headaches in the last year unrelated to respiratory infection, head trauma, or hangover. If they gave an affirmative response to the above question then a structured verbal headache interview was administered by a trained research coordinator to determine the characteristics of each headache type. The structured headache interview has been previously validated for the diagnosis of migraine and other headache disorders.[15] The research coordinators performing the diagnostic headache interviews were blinded to the atopic status and rhinitis diagnosis of the participant at the time of the interview.

Participants were later assigned a headache diagnosis by a board certified headache specialist based on information obtained from the headache interview. All classifiable headache diagnoses met strict criteria of the International Classification of Headache Disorders-II-2004.[16] Migraine headache was defined as ICHD-2 diagnoses of 1.1-1.5. The headache specialist was also blinded to the atopic status and rhinitis diagnosis of the participant.

The research coordinators queried participants on the frequency, duration, and severity of each different headache type. The frequency of migraine headache was defined as the number of days per month that a participant experienced a given headache type that later met diagnostic criteria for migraine headache. If a participant reported two headache types that both met diagnostic criteria for migraine headache then the headache with the highest reported frequency was used as the migraine frequency for that patient.

Those suffering from headache disorders completed the Migraine Disability Assessment (MIDAS) questionnaire. This validated written questionnaire assessed the number of days per 3 months with headache-related disability.[17] In participants receiving a diagnosis of migraine headache from the headache interview the MIDAS score defined their degree of migraine headache disability.

Additional data abstracted from the subject's medical records included the allergist's rhinitis (eg, allergic or mixed) and asthma diagnoses, seasonality of rhinitis symptoms (eg, perennial, seasonal, or both), results of skin prick and Immunocap allergy testing, and the current use of immunotherapy. We estimated the duration of immunotherapy through self-report of the start date of immunotherapy by the participant and/or chart review. A current medication list was obtained by either chart review or direct patient interview. Medications were grouped into migraine abortives (eg, triptans, ergots, butalbital-

containing medications, narcotics, nonsteroidal anti-inflammatories, and isometheptane/acetameniphen compounds), migraine preventatives (eg, beta blockers, calcium channel blockers, antidepressants, anticonvulsants, angiotensin converting enzyme inhibitors, angiotension II receptor blockers), rhinitis medications (eg, oral antihistamines, intranasal antihistamines or corticosteroids, mast cell stabilizers, and leukotriene modifiers) and asthma medications (eg, short- and long-acting beta 2 agonists, oral and inhaled corticosteroids, leukotriene modifiers).

All subjects underwent allergy testing with either skin prick or Immunocap (eg, serologic tests that identify IgE antibodies to specific common seasonal and perennial aeroallergens) tests. A battery of 20 allergens indigenous to the Cincinnati area were tested in the majority of subjects and included the following: (1) trees: American sycamore, American elm, red cedar, box elder, white oak, white ash, cottonwood, and red mulberry; (2) grasses: Timothy and meadow fescue; (3) weeds: short ragweed and English plantain; (4) indoor insects: dust mite mix, German cockroach; (5) animal: cat and dog epithelium; (6) indoor molds: *Cladosporium*, *Aspergillus mix*, and *Penicillium*; (7) outdoor mold: *Alternaria*. Percent allergic sensitization was defined as the number of positive allergy tests from the skin prick or Immunocap testing divided by the total number of allergy tests. Participants were later grouped into low and high atopic groups based upon specific cut points of allergen sensitization determined from the statistical analyses described below. A low atopic group was defined as those with a percent allergic sensitization of ≤45% and a high atopic group was defined as those with a percent allergic sensitization of >45%.

STATISTICS

Descriptive tables were generated showing the demographic and clinical characteristics of 536 participants stratified by migraine status (migraineur, nonmigraineur) and 174 migraineurs stratified by age (eg, ≤45 and >45 years of age). Justification for the age stratification is provided below. Differences between subject groups were assessed by chi-square tests.

The primary analysis investigated the effect of an increase in allergic sensitization and immunotherapy on migraine prevalence among 536 atopic subjects with allergic rhinitis subtypes (eg, diagnoses of allergic or mixed rhinitis). Migraine prevalence was analyzed by logistic regression. The model included linearly modeled percent allergic sensitization (percent positive out of a total of 20 allergens), immunotherapy (yes/no), allergic medication (yes/no), and gender.

Secondary analyses of 174 atopic migraineurs investigated the effects of increased allergic sensitization and immunotherapy on migraine frequency and MIDAS scores. Generalized additive models and plots of spline curves fitted to each dependent variable showed a nonlinear effect of increased allergic sensitization. A linear spline was analyzed which allowed slopes to differ above and below 45% allergic sensitization. In addition, analyses were stratified by age, as preliminary analyses had shown that there were differences in the slopes for increased allergic sensitivity in migraineurs less than and greater than 45 years of age (Fig. 1). The age stratae used in the analysis were not established a priori. Migraine frequency (days per month with migraine) was analyzed by Poisson regression. A bar graph showing risk ratios (RRs) associated with increasing levels of allergic sensitization was generated for participants less than 45 years of age. MIDAS scores were analyzed assuming a zero-inflated negative binomial distribution. This methodology was used in order to allow for an excess number of zero MIDAS scores, and to model the larger variability of MIDAS scores than the Poisson model allows. For both outcomes, the age-specific models included percent allergic sensitization for those with <45% and ≥45% allergic sensitization (modeled continuously), immunotherapy (yes/no), allergic medication (yes/no), migraine preventative medication (yes/no) and gender. The analyses were performed using SAS for Windows, Version 9.2 (SAS Institute, Cary, NC, USA). P values < 0.05 were considered significant.

RESULTS

Demographics.—A total of 536 participants with a diagnosis of an allergic rhinitis subtype participated

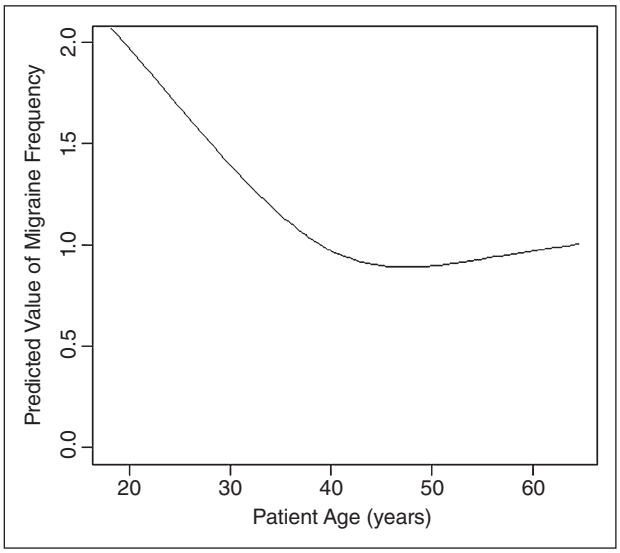

Fig. 1.—A smooth curve of predicted frequencies of migraine vs age for 174 patients with migraine headache. Note that prior to age 45 there is an inverse relationship between the predicted frequencies of migraine headache and age; after age 45 there is a slight positive relationship. These relationships provided a justification to stratify our analyses based on age. Only the lower part of this graph is shown to more clearly demonstrate the cut point of 45 years of age.

in this study. The mean age of the study population was 40.9 years of age and 60% of the participants were women. The mean percent allergic sensitization was 37% in the total population. The most common allergens to which subjects were sensitized included trees in 66%, grasses in 63%, weeds in 69%, and indoor insects in 63%. Forty-six percent of participants were receiving immunotherapy and the mean duration of immunotherapy was 4.95 years.

Table 1 subcategorized participants into those with and without a diagnosis of migraine headache (eg, migraineurs vs nonmigraineurs). The demographic variables and clinical characteristics were similar between the 2 groups with several exceptions. Migraineurs were more likely to be female than nonmigraineurs (73% vs 52%; $P < .01$). They also had a slightly higher rate of sensitization to tree allergens (69% vs 60%; $P = .046$).

The prevalence of migraine headache in the total population was 32.5%. The mean frequency of migraine was 3.39 days/month and the mean MIDAS score was 12.6 days of disability per 3 month time period. The mean duration of migraine attacks was 1.49 days and the mean severity (0-10 rating scale) was 7.36. Forty-four percent were receiving migraine abortive medications and 21% were receiving migraine preventives.

Table 2 shows the demographics and clinical characteristics of 174 migraineurs stratified by age (eg, ≤ and >45 years of age). Subjects >45 years of age were less likely to have positive allergy tests for grasses (46% vs 66%; $P < .01$), more likely to receive immunotherapy (54% vs 35%; $P < .01$) and had a longer duration of immunotherapy (3.70 years vs 2.77 years; $P = .03$). They also had a lower frequency of migraine headache (2.52 vs 3.89; $P = .08$) and were more likely to receive a diagnosis of "typical aura with migraine" (24% vs 14%; $P = .08$), but the results did not reach statistical significance.

Prevalence of Migraine Headache.—The prevalence of migraine headache was not altered by increasing degrees of allergic sensitization (OR = 0.95; 95% CI = 0.87, 1.03) (Table 3). Female participants were significantly more likely to have a diagnosis of migraine headache than male subjects (OR = 2.45; 95% CI 1.64, 3.66). There was a significant immunotherapy/age interaction ($P = .02$). The odds ratio for migraine prevalence was 1.06 (95% CI; 0.94, 1.20) for each 5-year increase of age in the immunotherapy group and 0.89 (95% CI; 0.80, 0.97) in the nonimmunotherapy group. The interaction is graphically depicted in Figure 2. Note that the model-adjusted prevalences are lower in the immunotherapy group than in the nonimmunotherapy group up to age 40. After age 40, the relationship changes and the model-adjusted prevalences are higher in the immunotherapy group than the nonimmunotherapy group.

Frequency of Migraine Headache.—This analysis included 174 migraineurs stratified by age. There were 111 migraineurs in the younger age strata (eg, ≤45 years of age) and 63 in the older age strata (eg, >45 years). Significant results, however, were observed only in the younger age strata (Table 4). The frequency of migraine headache decreased in those ≤45 years of age with increasing degrees of allergic sensitization in the low atopic group (<45% allergic sensitization) while it increased with increasing degrees of allergic sensitization in those in the high atopic group (≥45% allergic sensitization). The RR was 0.80 (95%

Table 1.—Demographics and Clinical Characteristics of 174 Migraineurs and 362 Nonmigraineurs

Demographics	Migraineurs (n = 174)	Nonmigraineurs (n = 362)	*P* Value¶¶
Female gender, n (%)	127 (73%)	190 (52%)	<.01
Mean age (years)	40.3	41.2	.39
Mixed rhinitis, n (%)	48 (28%)	96 (27%)	.79
Seasonality of rhinitis, n (%)†			
Perennial	33 (19%)	73 (20%)	.74
Seasonal	14 (8%)	36 (10%)	.48
Both perennial and seasonal	127 (73%)	252 (70%)	.42
Mean percent allergic sensitization‡	35%	38%	.20
Allergic sensitization, n (%)§			
Trees	103 (60%)	243 (69%)	.046
Grasses	101 (59%)	227 (64%)	.20
Weeds	115 (66%)	254 (71%)	.30
Indoor insects	105 (60%)	230 (64%)	.38
Animals	92 (53%)	199 (56%)	.60
Outdoor molds	52 (31%)	107 (31%)	.98
Indoor molds	27 (16%)	78 (22%)	.09
Immunotherapy, n (%)¶	76 (44%)	168 (47%)	.57
Mean duration of immunotherapy (years)††	3.2	6.5	.01
Duration of immunotherapy††			
0-3 months	11 (15%)	12 (15%)	.10§§
3-12 months	22 (31%)	15 (19%)	
1-5 years	24 (34%)	23 (29%)	
5 years	14 (20%)	29 (37%)	
Asthma, n (%)	35 (20%)	90 (25%)	.22
Medication use, n (%)‡‡			
Rhinitis meds	134 (77%)	268 (74%)	.80
Asthma meds	171 (32%)	122 (34%)	.20

†Perennial = rhinitis symptoms occur year around, but not seasonally, seasonal = rhinitis symptoms occur seasonally, but not year round, perennial + seasonal = rhinitis symptoms occur year around, but also worsen seasonally.
‡Mean percent positive allergy tests within a group of patients.
§Percent of participants with 1 or more positive allergy tests from the following groups of allergens: trees, grasses, weeds, indoor insects, animal, indoor molds, outdoor molds.
¶The number and percent of participants that were administered immunotherapy (yes/no) in each group.
††Data on the duration of immunotherapy were only obtained in 150 of the participants (71 migraineurs and 79 nonmigraineurs).
‡‡Percent of participants with use of 1 or more meds from the following categories of medications: rhinitis and asthma medications.
§§*P* value tests the equality of distributions of immunotherapy durations between migraineurs and nonmigraineurs.
¶¶*P* values compare variables between migraineurs and nonmigraineurs.

CI = 0.65, 0.991) for each 10% increase in allergic sensitization in the low atopic group and 1.60 (95% CI = 1.11, 2.29) in the high atopic group. Figure 3 depicts that the model-adjusted RRs for the frequency of migraine headache in those ≤45 years of age with increasing degrees of allergic sensitization. Note that RRs range from 1.03 to 0.42 in the low atopic group and 0.42 to 4.38 in the high atopic groups. Those receiving immunotherapy had an RR 0.48 (95% CI = 0.28, 0.83) for the frequency of migraine headache. The use of migraine preventatives and allergic medications did not influence the frequency of migraine headaches (Table 4).

Disability of Migraine.—This analysis was conducted in the same subgroups of participants utilized for the analysis of migraine frequency. Significant results were only seen in the younger age strata. The disability of migraine was inversely correlated to percent allergic sensitization in the low atopic group (≤45% sensitization), but was unchanged in the high

Table 2.—Demographics and Clinical Characteristics of 174 Migraineurs Stratified by Age

Demographics	Migraineurs: Age (Years) ≤ 45 (N = 111)	Migraineurs: Age (Years) > 45 (N = 63)	*P* Value†
Female gender, n (%)	78 (70%)	49 (78%)	.28
Prevalence of migraine subtypes			
Migraine without aura	97 (87%)	54 (86%)	.75
Typical aura with migraine	15 (14%)	15 (24%)	.08
Chronic migraine	6 (5%)	1 (2%)	.42
Probable migraine	24 (22%)	10 (16%)	.36
Mean frequency of migraine (days/month)	3.9	2.5	.08
Mean MIDAS scores (days/3 months)	13.1	11.7	.70
Mean duration of migraine (days)	1.5	1.4	.70
Mean severity of migraine (0-10 scale)	7.4	7.3	.91
Medication use, n (%)‡			
Migraine abortives	49 (44%)	27 (43%)	.87
Migraine preventatives	16 (14%)	21 (33%)	<.01
Allergic sensitization, n (%)§			
Trees	65 (60%)	38 (61%)	.83
Grasses	72 (66%)	29 (46%)	.01
Weeds	72 (65%)	43 (68%)	.65
Indoor insects	70 (63%)	35 (56%)	.33
Animals	57 (52%)	35 (56%)	.64
Outdoor molds	31 (29%)	21 (34%)	.48
Indoor molds	18 (17%)	9 (15%)	.73
Immunotherapy, n (%)¶	39 (35%)	37 (59%)	<.01
Mean duration of immunotherapy (years)††	2.8	3.7	.03
Duration of immunotherapy††			
0-3 months	7 (19%)	4 (11%)	.25‡‡
3-12 months	13 (36%)	9 (26%)	
1-5 years	12 (33%)	12 (34%)	
>5 years	4 (11%)	10 (29%)	

†*P* values compare variables between migraineurs in the 2 age stratae (eg, ≤ and >45 years of age).
‡Percent of participants with use of 1 or more meds from the following categories of medications: migraine abortive and migraine preventative medications.
§Percent of participants with 1 or more positive allergy tests from the following groups of allergens: trees, grasses, weeds, indoor insects, animal, indoor molds, outdoor molds.
¶The number and percent of participants that were administered immunotherapy (yes/no) in each group.
††Data on the duration of immunotherapy were obtained in 71 of the migraineurs (36 that were ≤45 years of age and 35 that were >45 years of age).
‡‡*P* value tests the equality of distributions of immunotherapy durations between migraineurs lesser and greater than 45 years of age.
MIDAS = Migraine Disability Assessment.

atopic group (>45% sensitization) in those ≤45 years of age that experienced migraine headache. The RR was 0.81 (95% CI = 0.68, 0.97) for each 10% increase in allergic sensitization in the low atopic group and was 1.14 (95% CI = 0.81, 1.58) in the high atopic group. Those receiving immunotherapy had an RR of 0.55 (95% CI = 0.35, 0.86) for migraine disability (Table 5).

DISCUSSION

This is the first study to determine if the degree of allergic sensitization and the administration of immunotherapy are associated with the prevalence, frequency, and disability of migraine headache in subjects with allergic rhinitis subtypes (eg, allergic or mixed rhinitis). Past studies have assumed that the

Table 3.—Odds Ratios and 95% CI of Migraine Prevalence in 536 Participants

Independent variable	OR	95% CI		*P* Value
Immunotherapy/age interaction				.02
Immunotherapy (yes): increasing age	1.06†	0.94	1.20	.36
Immunotherapy (no): increasing age	0.89†	0.80	0.97	.01
Mean percent allergic sensitization	0.95‡	0.87	1.03	.21
Rhinitis medicine (yes)	1.00	0.65	1.56	.99
Gender (female)	2.45	1.64	3.66	.01

†Represents the odds ratio for the prevalence of migraine headache for a 5-year increase in age in those receiving and not receiving immunotherapy.
‡OR of migraine headache being present vs absent corresponding to an increase in the percent positive allergy tests of 10%.

effect of allergy on migraine headache is uniform across all atopic patients. Our results suggest that the associations between allergy and migraine headache may depend upon the degree of allergic sensitization, administration of immunotherapy, patient age, and the type of headache outcome measures that are studied.

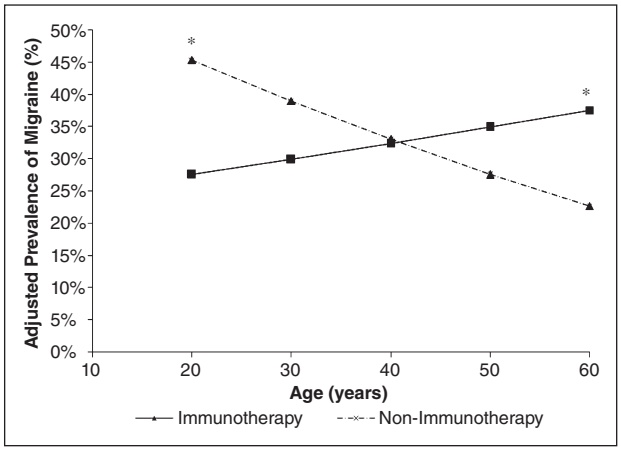

Fig. 2.—An immunotherapy/age interaction for the model-adjusted prevalences of migraine headache. The prevalences are lower up to age 40 in patients on immunotherapy compared with patients not on immunotherapy, and higher above age 40. Asterisks (*) indicate that the prevalences are significantly different ($P < .05$) between the immunotherapy and nonimmunotherapy groups at 20 and 60 years of age.

Table 4.—Risk Ratios (RRs) and 95% CI of Migraine Frequency Stratified by Age†

Model I: Age ≤ 45 Years				
Independent Variable	RR	95% CI		*P* Value
Allergic sensitization‡				
≤45%	0.80‡	0.65	0.99	.04
>45%	1.60‡	1.11	2.29	.01
Immunotherapy (yes)	0.48	0.28	0.83	.01
Rhinitis medicines (yes)§	1.55	0.72	3.35	.26
Migraine preventatives (yes)§	0.98	0.48	2.04	.97
Gender (female)	0.72	0.37	1.38	.32
Model II: Age > 45 Years				
Independent Variable	RR	95% CI		*P* Value
Allergic sensitization				
≤45%	0.92‡	0.72	1.17	.48
>45%	1.37‡	0.87	2.18	.18
Immunotherapy (yes)	1.00	0.56	1.77	1.00
Rhinitis medicines (yes)§	0.90	0.39	2.08	.81
Migraine preventatives (yes)§	1.82	0.66	5.02	.24
Gender (female)	1.99	0.83	4.78	.13

†These analyses were conducted in 174 migraineurs stratified by age. There were 111 participants in the ≤45 years of age strata and 63 in the >45 years of age strata.
‡The RRs for migraine frequency corresponding to an increase in allergic sensitization of 10%.
§Modeled as the presence of 1 or more medications from the following categories of medications: rhinitis medicines (yes/no) and migraine preventatives (yes/no).

Degree of Allergic Sensitization.—The degree of allergic sensitization in our study was not associated with the prevalence of migraine headache. It is tempting to speculate from these results that atopy does not play any role in the prevalence of migraine headache and that our results differ from those obtained from population-based studies which have reported an increased prevalence of migraine headache in patients with allergic rhinitis and hay fever.[4-6] However, our study was not designed to determine if the "presence or absence" of allergic rhinitis increased the prevalence of migraine headache. Our results only imply that there is no clear dose-response relationship between the "degree of atopy" and the prevalence of

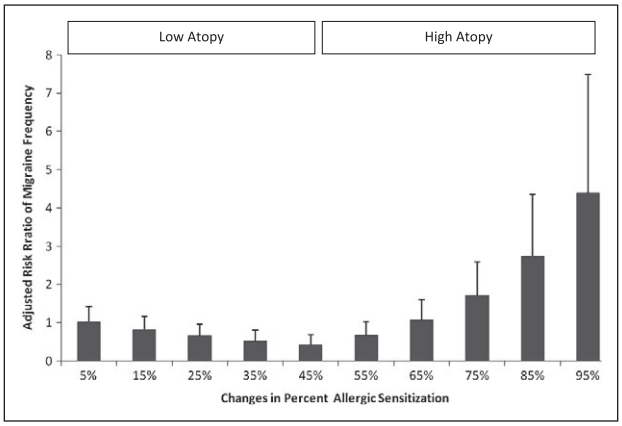

Fig. 3.—Graph showing the model-adjusted risk ratios of migraine frequency with increasing degrees of allergic sensitization in 111 migraineurs ≤45 years of age. Each 10% increase in percent allergic sensitization leads to a decrease in the risk ratio for allergic sensitization in the low atopy group (n = 78). This relationship changes in the high atopy group (n = 33) with each 10% increase leading to an increase in the risk ratios for migraine frequency.

migraine headache in subjects with an allergic rhinitis component.

Migraine frequency was associated with the degree of allergic sensitization, but only in participants less than 45 years of age. The direction and magnitude of the association differed in the low and high atopic groups. A lower frequency of migraine headaches was observed with increasing percentages of positive allergy tests in the low atopy group (<45% allergic sensitization) while a higher frequency of migraine headache was observed with increasing percentages of positive allergy tests in the high atopy group (≥45% allergic sensitization). This could suggest that there is a "threshold" below which increasing degrees of allergic sensitization are preventative and above which they are provocative for migraine headache. The magnitude of the effect would appear to be most pronounced in the high atopic group with RRs ranging from 0.42 at 45% sensitization to 4.38 at 95% sensitization, but these results should be interpreted cautiously as there was a modest number of migraineurs in the high atopic group (n = 33).

Migraine disability followed a similar pattern to that observed with migraine frequency within participants ≤45 years of age. Migraine disability decreased with increasing percentages of positive allergy tests in the low atopic group. It increased with increasing percentages of positive allergy tests in the high atopic group, but these results did not reach statistical significance. This could imply that increasing degrees of allergic sensitization may prevent migraine disability in those with overall lower degrees of atopy (≤45% allergic sensitization).

Table 5.—Risk Ratios (RR) and 95% CI for Migraine Disability Stratified by Age†

Model I: Age ≤ 45 Years				
Independent Variable	RR	95% CI		*P* Value
Allergic sensitization‡				
≤45%	0.81‡	0.68	0.97	.02
>45%	1.14‡	0.81	1.59	.47
Immunotherapy (yes)	0.55	0.35	0.87	.01
Rhinitis medicines (yes)	1.28	0.78	2.12	.33
Migraine preventatives (yes)§	1.14	0.64	2.04	.65
Gender (female)	1.84	1.17	2.90	.01
Model II: Age > 45 Years				
Independent Variable	RR	95% CI		*P* Value
Allergic sensitization				
≤45%	1.04‡	0.75	1.44	.81
>45%	0.98‡	0.65	2.07	.97
Immunotherapy (yes)	1.07	0.55	2.10	.84
Rhinitis medicines (yes)§	0.75	0.26	2.17	.59
Migraine preventatives (yes)§	0.63	0.31	1.29	.20
Gender (female)	1.74	0.64	4.70	.28

†Migraine disabilities were measured by obtaining MIDAS scores in 174 migraineurs stratified by age (111 participants were ≤45 and 63 were >45 years of age).
‡The RRs for migraine disability corresponding to an increase in allergic sensitization of 10%.
§Modeled as the presence of 1 or more medications from the following categories of medications: rhinitis medicines (yes/no) and migraine preventatives (yes/no).
MIDAS = Migraine Disability Assessment.

Immunotherapy.—The administration of immunotherapy and its relationship to the prevalence of migraine headache is one of the more interesting findings of the entire study. Younger migraineurs receiving immunotherapy had lower prevalence rates of migraine headache than those not receiving immuno-

therapy. Conversely, older subjects receiving immunotherapy had higher prevalence rates than those not receiving this therapy. This association was independent of the degree of atopy, gender, and use of rhinitis medications. This could suggest that age modulates the effect of immunotherapy on the prevalence of migraine headache with immunotherapy decreasing prevalence at younger ages and increasing it at older ages.

Our models predict a 52% reduction in the frequency of migraine headache and a 45% reduction of the number of days with migraine-related disability in migraineurs ≤45 years of age that received immunotherapy. These results are consistent with several past case series that have reported a decreased frequency of headache in atopic patients receiving immunotherapy.[12,14,18] If future prospective studies confirm these results, then immunotherapy could be employed to decrease the frequency and disability of migraine headache in younger migraineurs.

There are several mechanisms through which immunotherapy could modulate migraine headache. First, immunotherapy increases the production of IL-10 by T_{reg} cells, which reduces the release of proinflammatory cytokines from mast cells, decreases the number of mast cells and prevents mast cell degranulation.[11] Thus, the overall effect of immunotherapy might be to down-regulate mast cells. Second, it blunts the immunologic response to allergens that may be triggers for migraine headache. Immunotherapy reduces allergen-specific IgE production and allergen stimulated T cell proliferation. It also suppresses type 2 T helper cells, which are critical to the allergic response, and induces allergen-specific IgG and IgA that block binding of IgE to mast cells.[11]

Age.—Our data demonstrated that atopy was only associated with migraine outcome measures at younger ages (≤45 years of age) suggesting that atopy may play less of a modulatory role in an older population. Such a hypothesis is bolstered by a population-based study demonstrating that the number of positive allergy tests peaks at 20 years of age and declines thereafter.[19] This could be secondary to a natural decline of adaptive immunity with aging. Studies have found decreased function of B cells,[20] T cells[21,22] and eosinophils[23,24] in geriatric populations. These alterations could decrease the allergic response and make allergens less likely to influence migraine headache in older individuals.

Allergy and Migraine Pathogenesis.—The allergic response involves the uptake of allergens by antigen presenting cells (ie, macrophages, dendritic cells) that break down these allergens to small peptides that are presented in the context of MHC Class II molecules to T cells. These T cells release various cytokines that determine the type of specific T helper cell subtypes into which they differentiate (eg, Th1, Th2, Th9, and Th17 cells). Th2 cells produce cytokines such as IL-4 and IL-13 that lead to the synthesis and release of allergen-specific IgE from B cell derived plasma cells. The specific IgE then binds to high affinity IgE receptors on mast cells or basophils. Upon reexposure to the specific allergen, the relevant allergenic peptide is recognized by antigen binding sites on the specific IgE antibodies affixed to the mast cells. Then the mast cells become activated and release bioactive mediators (ie, histamine, proteinases [eg, tryptase], serotonin, leukotrienes, prostaglandins, etc) leading to the physiologic changes associated with allergic disease.[25,26]

It is conceivable that allergens could activate trigeminal afferents through enhanced release of inflammatory mediators from dural mast cells.[27,28] Mast cells reside in close proximity to trigeminal afferents located in the dura of both humans and rodents.[29] Levy et al[27] have reported in animal models that degranulation of mast cells by compound 48/80 can activate trigeminal afferents and increase c fos expression within the spinal trigeminal nucleus caudalis. Markowitz et al[30] sensitized guinea pigs with an allergen (eg, ovalbumin) 6 weeks prior to experimentation and then reexposed them to this compound. Five minutes after exposure the animals were sacrified and found to have greater amounts of dural protein plasma extravasation compared with controls. These experimental studies suggest that degranulation of dural mast cells can activate trigeminal nociceptors and that systemic exposure to an allergen can induce protein plasma extravasation within the dura, which likely resulted from mast cell activation.

The above results indicate that there may be a paradoxical effect of atopy on the frequency and disability of migraine headache in younger individuals. Given that an increased frequency of migraine headache was only observed in subjects in our high atopy group it is possible that only the "highest" degrees of atopy are provocative for migraine headache. Those with greater percentages of positive allergy tests would have a greater number of allergens to provoke an allergic response, which could theoretically increase the frequency and disability of migraine headache. Lower degrees of atopy might provide a modest preventative effect through mechanisms yet to be defined. It is also quite possible that the high and low atopic groups represent different migraine phenotypes.

Atopy and Migraine Headache.—Atopic symptoms commonly present in patients with migraine headache. Sillanpaa et al[31] reported that 39.5% of boys and 46.2% of girls (age range of 7-22 years of age) with migraine headache reported allergy symptoms. Artto et al[32] found that 25.4% of men and 37.4% of women with migraine headache reported a past history of atopy.

What might our data imply about the relationship between atopy and migraine headaches? The lack of a simple linear relationship between the degree of allergic sensitization and migraine frequency and disability does not preclude the possibility that allergy plays a role in migraine headache. It only suggests that the degree of allergic sensitization has a different effect on these outcome measures in those patients with high and low degrees of atopic. In fact, the greatest evidence from our study that allergy does indeed play a role in migraine headaches is that modulation of the allergic response with immunotherapy is associated with a decreased prevalence, frequency, and disability of migraine headaches in younger patients. The optimal study to answer the above question would be one in which the frequency, severity, and disability of migraine headaches are compared in those with and without allergic rhinitis.

We found that the degree of atopic sensitization was associated with migraine frequency and disability in patients ≤45 years of age, but had no association with migraine prevalence. It is quite possible that factors that modulate frequency and disability might be different from those that modulate prevalence. This could suggest that the degree of allergic sensitization is more modulatory for migraine (eg, influencing frequency and disability) than causative (eg, modulating the presence or absence of migraine).

Advantages and Limitations of Study.—Our study offers several advantages to past studies that explored the relationship between allergic rhinitis and migraine headache. First, investigating a chronic allergic rhinitis population in an allergy specialty setting represented an ideal population as all subjects were already characterized as to their atopic status and allergic rhinitis diagnosis. Second, use of a validated verbal diagnostic headache interview allowed accurate and reliable diagnoses of migraine headache and other headache disorders. It also enabled us to tease out the clinical characteristics of multiple headache types that often coexist in headache patients. Third, we controlled for factors such as use of immunotherapy, rhinitis medications, migraine preventatives, gender, and age that could impact the associations observed in our analyses. Fourth, we used validated headache outcome measures for migraine frequency and disability. McKenzie et al[33] found that the self-reported monthly frequency of headache is highly correlated with headache frequencies obtained from a daily headache diary. Likewise, the MIDAS questionnaire has also been validated against daily estimates of headache-related disability.[17]

There are several limitations to our study worth noting. First, our allergy testing included primarily airborne allergens and not food allergens as food allergy testing is not indicated unless there is a history to suggest a food allergy. Therefore, our results involving allergic sensitization may not apply to subjects with a history of confirmed food allergy. Second, these results apply to allergic rhinitis patients in a subspecialty allergy practice and may not generalize to other populations. Third, this was a cross-sectional study and therefore causal inferences cannot be made from such data. Fourth, immunotherapy is often administered along with other cotherapies such as rhinitis medications and instructions on avoidance

of allergens. Thus, any influence of immunotherapy on headache outcome measures may be the combined effect of several therapies. Fifth, 28% of our patients had mixed rhinitis, which is a type of rhinitis with both allergic and nonallergic (eg, perfumes, gasoline, paint, etc) triggers. As our study only investigated the burden of allergic triggers, we cannot rule out the possibility that nonallergic triggers could also be associated with the prevalence, frequency, and disability of migraine headache.

CONCLUSIONS

Our study found that the administration of immunotherapy is associated with a decreased prevalence, frequency, and disability of migraine headache in younger subjects. Furthermore, migraine headaches are less frequent and less disabling in younger migraineurs (eg, age < 45 years of age) with low degrees of allergic sensitization and more frequent in those with higher degrees of allergic sensitization. These findings suggest that atopy is most provocative for attacks of migraine headache in patients with the "highest" degrees of atopy and that immunotherapy and atopy affect migraine headache to a greater degree in younger than older migraineurs. It is clear from our study that further investigations into the interrelationships between allergy and migraine headache are warranted.

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REFERENCES

1. Lipton RB, Stewart WF, Diamond S, Diamond ML, Reed M. Prevalence and burden of migraine in the United States: Data from the American Migraine Study II. *Headache.* 2001;41:646-657.
2. Gergen PJ, Turkeltaub PC. The association of individual allergen reactivity with respiratory disease in a national sample: Data from the second National Health and Nutrition Examination Survey, 1976-80 (NHANES II). *J Allergy Clin Immunol.* 1992;90:(4 Pt 1):579-588.
3. Nathan RA, Meltzer EO, Derebery J, et al. The prevalence of nasal symptoms attributed to allergies in the United States: Findings from the burden of rhinitis in an America survey. *Allergy Asthma Proc.* 2008;29:600-608.
4. Ku M, Silverman B, Prifti N, Ying W, Persaud Y, Schneider A. Prevalence of migraine headaches in patients with allergic rhinitis. *Ann Allergy Asthma Immunol.* 2006;97:226-230.
5. Aamodt AH, Stovner LJ, Langhammer A, Hagen K, Zwart JA. Is headache related to asthma, hay fever, and chronic bronchitis? The Head-HUNT Study. *Headache.* 2007;47:204-212.
6. Mortimer MJ, Kay J, Gawkrodger DJ, Jaron A, Barker DC. The prevalence of headache and migraine in atopic children: An epidemiological study in general practice. *Headache.* 1993;33:427-431.
7. Crystal-Peters J, Neslusan CA, Smith MW, Togias A. Health care costs of allergic rhinitis-associated conditions vary with allergy season. *Ann Allergy Asthma Immunol.* 2002;89:457-462.

8. Mansfield LE, Vaughan TR, Waller SF, Haverly RW, Ting S. Food allergy and adult migraine: Double-blind and mediator confirmation of an allergic etiology. *Ann Allergy.* 1985;55:126-129.
9. Monro J, Brostoff J, Carini C, Zilkha K. Food allergy in migraine. Study of dietary exclusion and RAST. *Lancet.* 1980;2:1-4.
10. Grant EC. Food allergies and migraine. *Lancet.* 1979;1:966-969.
11. Akdis M. Immune tolerance in allergy. *Curr Opin Immunol.* 2009;21:700-707.
12. Weil AJ. Familial atopic rhinitis and cephalea. *Ann Allergy.* 1972;30:424-427.
13. Shapiro RS, Eisenberg BC. Allergic headache. *Ann Allergy.* 1965;23:123-126.
14. Lehrer JF, Silver J, Cordes BG. Headache associated with IgE-mediated allergy: Response to immunotherapy. *Ear Nose Throat J.* 1985;64:228-231.
15. Andrew ME, Penzien DB, Rains JC, Knowlton GE, McAnulty RD. Development of a computer application for headache diagnosis: The Headache Diagnostic System. *Int J Biomed Comput.* 1992; 31:17-24.
16. Headache Classification Subcommittee of the International Headache Society. The International Classification of Headache Disorders (2nd Edition). *Cephalalgia.* 2004;24(Suppl. 1):24-36.
17. Stewart WF, Lipton RB, Kolodner KB, Sawyer J, Lee C, Liberman JN. Validity of the Migraine Disability Assessment (MIDAS) score in comparison to a diary-based measure in a population sample of migraine sufferers. *Pain.* 2000;88:41-52.
18. Inhalation OH. Sensitization in allergic headache. *South Med J.* 1948;41:931.
19. Barbee RA, Lebowitz MD, Thompson HC, Burrows B. Immediate skin-test reactivity in a general population sample. *Ann Intern Med.* 1976;84:129-133.
20. Allman D, Miller JP. The aging of early B-cell precursors. *Immunol Rev.* 2005;205:18-29.
21. Weng NP. Aging of the immune system: How much can the adaptive immune system adapt? *Immunity.* 2006;24:495-499.
22. Maue AC, Yager EJ, Swain SL, Woodland DL, Blackman MA, Haynes L. T-cell immunosenescence: Lessons learned from mouse models of aging. *Trends Immunol.* 2009;30:301-305.
23. Mathur SK, Schwantes EA, Jarjour NN, Busse WW. Age-related changes in eosinophil function in human subjects. *Chest.* 2008;133:412-419.
24. Gomez CR, Nomellini V, Faunce DE, Kovacs EJ. Innate immunity and aging. *Exp Gerontol.* 2008; 43:718-728.
25. Ozdemir C. An immunological overview of allergen specific immunotherapy – subcutaneous and sublingual routes. *Ther Adv Respir Dis.* 2009;3:253-262.
26. Akdis CA, Akdis M. Mechanisms and treatment of allergic disease in the big picture of regulatory T cells. *J Allergy Clin Immunol.* 2009;123:735-746; quiz 747-738.
27. Levy D, Burstein R, Kainz V, Jakubowski M, Strassman AM. Mast cell degranulation activates a pain pathway underlying migraine headache. *Pain.* 2007;130:166-176.
28. Theoharides TC, Donelan J, Kandere-Grzybowska K, Konstantinidou A. The role of mast cells in migraine pathophysiology. *Brain Res Brain Res Rev.* 2005;49:65-76.
29. Artico M, Cavallotti C. Catecholaminergic and acetylcholine esterase containing nerves of cranial and spinal dura mater in humans and rodents. *Microsc Res Tech.* 2001;53:212-220.
30. Markowitz S, Saito K, Moskowitz MA. Neurogenically mediated plasma extravasation in dura mater: Effect of ergot alkaloids. A possible mechanism of action in vascular headache. *Cephalalgia.* 1988;8:83-91.
31. Sillanpaa M, Aro H. Headache in teenagers: Comorbidity and prognosis. *Funct Neurol.* 2000;15(Suppl. 3):116-121.
32. Artto V, Wessman M, Nissila M, et al. Comorbidity in Finnish migraine families. *J Headache Pain.* 2006;7:324-330.
33. McKenzie JA, Cutrer FM. How well do headache patients remember? A comparison of self-report measures of headache frequency and severity in patients with migraine. *Headache.* 2009;49:669-672.