

DR. Yael GRAIF (Orcid ID : 0000-0001-8004-9477)

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Association between Asthma and Migraine - A Cross-Sectional Study of over 110,000 Adolescents

Yael Graif, MD*; Tamy Shohat, MD, MPH^{†‡}; Yossy Machluf, PhD^{§#};
Rivka Farkash, BSc, MPH^{||}; Yoram Chaiter, MD, MSc[§]

**Allergy and Immunology Clinic, Pulmonary Institute, Rabin Medical Center, Petach Tikva, affiliated with Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel*

†Israel Center for Disease Control, Ministry of Health, Ramat Gan, Israel

‡Department of Epidemiology and Preventive Medicine, Sackler Faculty of Medicine, Tel Aviv University Medicine, Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel

§Medical Corps, Israel Defense Forces, Tel Hashomer, Israel

#Shamir Research Institute, Haifa University, Kazerin, Israel

||Shaare Zedek Medical Center, Jerusalem, Israel

Corresponding author: Yael Graif MD

Allergy and Immunology Clinic, Pulmonary Institute, Rabin Medical Center –
Beilinson Hospital, Petach Tikva 4941492, Israel. Tel: +972-54-4997850; Fax: +972-3-937-7142; E-mail: yael.graif@gmail.com

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Conflicts of interest

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Asthma; Allergic Rhinitis; Migraine; Headache; Sinusitis; Specialist; Risk Factor;

Abstract

Background: Epidemiological studies have reported an association between asthma and migraine, mainly in adults.

Objective: To examine the association between specialist-diagnosed asthma and migraine among adolescents.

Methods: The electronic database of a recruitment center was retrospectively searched for all 17-year-old draftees during the years 1987-2010. Diagnoses of asthma and migraine were made by certified specialists. The prevalence of migraine was compared among draftees with and without asthma. Covariate data on socio-demographics and associated medical conditions were recorded.

Results: A total of 113,671 adolescents were available for analysis. Asthma was diagnosed among 4.0% and migraine among 1.9%. Migraine was significantly more prevalent among adolescents with asthma [174 of the 4,581 subjects (3.8%)] compared to those without asthma [1,946 of the 109,090 (1.8%)] [OR=2.17 (95% CI 1.86-2.55; $P < 0.001$)]. Rates of migraine among subjects with and without allergic rhinitis were 6.3% and 1.7%, respectively [OR=4.04(95%CI 3.58-4.56; $P < 0.001$)]. On multivariate analysis, there was a significant association between migraine and both asthma [OR 1.42 (95% CI 1.19-1.68)] and allergic rhinitis [OR 3.18 (95% CI 2.80-3.63)]. Other factors significantly associated with migraine were female gender,

urban area of residence, recent immigration to Israel, having three or fewer siblings, and abnormal body mass index.

Conclusion: Clinicians should be aware that asthma and allergic rhinitis are potential risk factors for migraine in adolescents. A combined finding of these conditions and recurrent headache is highly suggestive of migraine and warrants a different diagnosis and treatment approach from sinusitis.

Introduction

Asthma and migraine are common chronic medical disorders. The prevalence of asthma has increased considerably in recent decades, and according to current estimates, more than 300 million people are affected worldwide.^{1,2} Migraine has a reported prevalence of about 11% in the adult population worldwide.³ Although asthma is a respiratory disorder and migraine is a neurologic disorder, the question of their relationship has fascinated allergists and neurologists for more than a century. Indeed, asthma has been previously described as "acephalic migraine" and "pulmonary migraine".^{4,5}

Population-based studies have reported an association between the two diseases,⁶⁻⁸ mainly in adults. A study on adolescents from the United States noted a physical comorbidity of migraine with inflammatory and other conditions and a significant association of migraine with higher rates of asthma and seasonal allergies.⁹

Asthma in adolescent is allergic in most cases¹⁰ and comorbidity of allergic asthma with migraine might be attributed to inflammatory mediators including histamine, tryptase, prostaglandins etc., produced by mast cells.¹¹ Mast cell degranulation activates a pain pathway underlying migraine headache.¹² Longitudinal studies have shown that the diagnosis of asthma preceded the development of chronic migraine. The American Migraine Prevalence and Prevention

(AMPP) Study has demonstrated that asthma was associated with an increased risk of new onset chronic migraine among individuals with episodic migraine¹³. In a large population based nationwide cohort study adult patients with asthma from Taiwan had 1.45- fold higher subsequent risk of migraine than those without asthma¹⁴.

We examined the association between specialist-diagnosed asthma and migraine in a large cross-sectional cohort of adolescents born between 1970 and 1993 in Israel. We controlled for potential confounders that were previously reported to be associated with asthma^{15,16}.

Methods

Data source

All data for the present study were extracted from the electronic database of an Israel Defense Forces (IDF) recruitment center in the northern district of Israel for 1987-2010. Army service is mandatory in Israel. All 17-year-old citizens (both genders) are required by law to present to the local military recruitment center for medical assessment and classification based on documentation from the subject's family physician, personal medical interview, and physical examination by members of the medical board. Subjects may be referred to specialists for further evaluation as necessary. The medical information is stored in the database together with personal and socio-demographic information from the Israel Population Registry. The northern district recruitment center was chosen for the present study because of the known comprehensiveness and reliability of its medical data.¹⁷

The study was approved by the IDF Institutional Review Board and Helsinki Committee.

Definitions of asthma, allergic rhinitis and migraine

All military candidates routinely submit a medical questionnaire completed by their family physician which includes questions on asthma, rhinitis and migraine, as well as documents from specialists when relevant. The medical evaluation by the physician's medical board includes a thorough interview during which the candidates are asked on various medical conditions; regarding the respiratory system, they are asked whether they had ever experienced wheezing, cough and/ or shortness of breath and whether they had ever been diagnosed with asthma. In addition, questions concerning the use of medications for treating asthma are assessed. If asthma is suspected, subjects undergo spirometry at rest and exercise and, in some cases, metacholine challenge test all in accordance with published guidelines of the American Thoracic Society¹⁸. A certified specialist in pulmonology reviews the data and makes the final diagnosis. Allergic rhinitis is defined as chronic seasonal or perennial rhinitis treated with combined medication (antihistamines and nasal steroids sprays). Migraine is defined as frequent typical headaches (presenting at least once a month over the past year) with or without aura. Candidates who report on migraine headaches are asked about the following: type of headaches, frequency and duration of the attacks as well as how long they are suffering from such headaches. When migraine is reported by the family physician or the candidate, the subject is referred to a certified specialist in neurology who makes a final diagnosis.

Definition of covariates

Socio-demographic variables included sex, age, weight, height, and calculated body mass index (BMI). The BMI category of each individual was determined using the age- and gender-related percentiles on the Israel Ministry of Health growth charts, similar to the approach used in the United States by the Centers for Disease Control

and Prevention, as follows: obese, >95th percentile(>28.2 kg/m² for males, >29.6 kg/m² for females); overweight, 85th - <95th percentiles (25.0-28.2 kg/m² for males, 25.2-29.6 kg/m² for females); underweight, <5th percentile (<17.6 kg/m² for males, <17.2 kg/m² for females); and normal weight.

Area of residence was categorized as rural or urban. A rural area was defined as a settlement with 2,000 residents or less, and an urban area, as a settlement with more than 2,000 residents, according to the criteria of the Israel Bureau of Statistics.

Statistical methods

Patient characteristics are described by proportions. Chi-square test was used to compare categorical variables between groups. Variables found to be significantly associated with outcome at a probability level of $P < 0.05$ on univariate analysis were entered in a multivariable logistic regression model. Odds ratios (OR) and 95% confidence intervals (95% CI) were calculated. All statistical tests were 2-sided. A P value of < 0.05 was considered statistically significant.

All data for the study were generated using the SPSS statistical package, version 22.0 (IBM Corp., Armonk, NY).

Results

Data on 113,671 adolescents, 66,547 male and 47,124 female, were available for analysis. The characteristics of the study participants are presented in table 1. Asthma was diagnosed in 4,581 subjects (4.0%), of whom 174 (3.8%) were also diagnosed with migraine. Among the 109,090 subjects without asthma, 1,946 (1.8%) were diagnosed with migraine. The difference in the rate of migraine in patients with and without asthma was statistically significant [OR=2.17 (95% CI 1.86-2.55), $P < 0.001$].

Separate analysis of patients with allergic rhinitis revealed that 6.3% were also diagnosed with migraine compared to 1.3% of subjects without allergic rhinitis [OR=4.04 (95%CI 3.58-4.56), $P < 0.001$].

Other factors significantly associated with migraine were female gender, living in an urban area, recent immigration to Israel, three or fewer siblings in the family, and abnormal BMI. The results are shown in Table 2.

On multivariable analysis, after adjustment for covariates (Table 3), independent risk factors for migraine were asthma [OR=1.42 (95%CI 1.19-1.68) $P < 0.001$] and allergic rhinitis [OR=3.18 (95%CI 2.8-3.63); $P < 0.001$]. Additional significant factors were female gender, living in urban area, recent immigration to Israel, three or fewer siblings in the family, and an abnormal BMI.

Discussion

This is the first large cross-sectional study on the association between asthma and migraine among adolescents that is based on diagnoses made by specialists in both fields (pulmonology and neurology). The major strength of this study is its sample size and consequent high statistical power.

The results showed that the adjusted estimated relative risk of adolescents with asthma to have a diagnosis of migraine was 1.42. Similarly, a Norwegian questionnaire-based study reported that both migraine and non-migrainous headaches were approximately 1.5-fold more likely to occur in people with asthma than in people without asthma.⁷ Conversely, in a study of migraine, a large matched case-control study from the United Kingdom based on the General Practice Research Database of subjects born from 1891 to 2000 reported a 1.59 relative risk of asthma in migraineurs compared to non-migraineurs.⁶ This value is close to that in the present study, although we investigated only subjects born from 1970 to 1993.

A study from Tawian, recently published in this Journal reported that migraine is associated with a significantly increased risk of asthma, mainly in the age group 40-60 and suggested that clinicians should consider migraine as a predisposing factor for asthma in the adult population.¹⁹

In a community study of adolescents from the United States, data derived from caretaker/parental self-reports indicated that subjects with migraine more frequently reported asthma and hay fever symptoms than subjects without migraine.⁹ Finally, a group from Turkey reported a higher prevalence of positive bronchial provocation tests in subjects with migraine than in controls and discussed the issue of inflammation in both pathologies.²⁰

Given the high rate of allergic as opposed to non-allergic asthma in children and young adults,^{21,22} we assume that the majority of the asthmatic adolescents in our study had allergic asthma. This is supported by a large earlier study by our group wherein 95.5% of asthmatic adolescents were found to have a positive skin prick test to at least one aeroallergen. In subjects whose pretest probability was low to moderate, a negative skin prick test decreased the probability of having asthma by 10- to 20-fold.¹⁰

In the present study, allergic rhinitis was strongly associated with migraine, and the OR was even higher than for asthma on multivariable analysis (3.18 vs 1.42). However, although the diagnosis of allergic rhinitis was made by family physicians, it was not always validated by skin tests and allergy specialists. By contrast, the diagnoses of asthma and migraine were made by specialists.

Allergists as well as otolaryngologists often encounter patients complaining of "sinus headache" who are found in at least half the cases to have migraine.²³⁻²⁵ Many studies have investigated the potential mechanism underlying the link between allergic rhinitis, asthma, and migraine, but the findings are not definitive. Immune

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mediators, cytokines, and neuropeptides may be implicated.²⁶ Attention has been directed specifically at transient receptor potential vanilloid subfamily member 1 (TRPV1), which has been shown to play a role in the pathophysiology of both asthma and migraine. The activation of TRPV1 in c-fiber sensory nerves in the airway leads to the manifestation of asthma features including bronchoconstriction, hypersecretion, and cough.²⁷⁻²⁹ It also lead to the release of neuropeptides at the peripheral termini of the trigeminal nociceptors which initiate neurogenic inflammation via their vasodilatory effect, culminating in a migraine attack.^{27,32}

Mast cell activity has also been investigated as a trigger of asthma, allergic rhinitis, and migraine. Mast cells produce inflammatory mediators such as histamine, tryptase and prostaglandins, and their role in allergic diseases is well established.³⁰ Intracranial mast cell degranulation also induces a prolonged state of excitation of the meningeal nociceptors, activating a pain pathway in migraine headache.^{31,32} Additionally, brain mast cells secrete pro-inflammatory and vasodilatory molecules in response to corticotropin-releasing hormone, a mediator of stress which is known to precipitate or exacerbate migraine.³¹ Clinically, migraine-like headache is part of the symptoms of mast cell activation syndrome.³³ A case control study in children conducted in Europe reported that history of anti-asthmatic or anti-allergic therapies was associated with decreased risk of migraine.³⁴

As this is a cross sectional study, the temporal sequence between asthma and migraine could not be determined. However, previous studies demonstrated that a diagnosis of asthma preceded the development of chronic migraine.^{13,14} Atopy, parasympathetic hyperactivity and enhanced neuropeptide release were given as examples for shared biological mechanisms for both conditions in those studies. However, these shared mechanisms did not contribute to the understanding of the suggested temporal sequence.

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In terms of additional factors, the present study found that female gender was a risk factor for migraine, in agreement with others.^{13,14} In addition, migraine was more prevalent in subjects with an abnormal BMI, particularly obese subjects, than those with normal BMI. Previous studies reported more chronic migraine in obese subjects.³⁵ A significant association was also found between migraine and area of residence (urban), having three or less siblings and being born outside of Israel. These covariates were previously reported to be associated with asthma^{16,17} but not with migraine. The magnitude of odds ratio associated with these covariates decreased in the multivariable analysis, suggesting they were indeed confounders.

The present study has some limitations. The data was analyzed retrospectively. As the information on asthma and migraine was collected in a cross sectional design, we could not infer temporal sequence or causality.

In conclusion, this large cross-sectional study revealed that adolescents with asthma or allergic rhinitis appear to have a significantly higher risk of migraine than those without these conditions. This may support the hypothesis that allergic asthma and rhinitis share a common pathophysiology with migraine. Findings of asthma or allergic rhinitis among adolescents who complain of recurrent headaches may indicate migraine, warranting a different diagnosis and treatment approach from sinusitis. Clinicians should suspect migraine more often in the differential diagnosis. Further investigation based on the known comorbidities and pathogenesis of asthma and migraine may lead to the development of new treatments for both diseases.

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Table 1. Characteristics of the study participants

Variable	N (%)
Gender	
Female	47,124 (41.5)
Male	66,547 (58.5)
Residence	
Urban	56,727 (49.9)
Rural	56,944 (50.1)
Origin	
Immigrant	18,032 (15.8)
Israel-born	95,639 (84.2)
No. of siblings	
≤3	52,023 (45.8)
>3	61,519 (54.2)
Body mass index	
Normal	91,043 (80.1)
Underweight	4,556 (4.0)
Overweight	11,750 (10.3)
Obese	6,322 (5.6)
Population group	
Jews	99,643 (87.7)
non-Jews	14,028 (12.3)

Table 2. The association of migraine with asthma, allergic rhinitis and patient characteristics (univariate analysis)

Variable	Migraine	No migraine	Odds ratio, 95% CI	<i>P</i> value
Asthma				
Yes	174 (3.8)	4,407 (96.2)	2.17 (1.86-2.55)	<0.0001
No	1,946 (1.8)	107,144 (98.2)	-	
Allergic rhinitis				
Yes	331 (6.3)	4,908 (93.7)	4.04 (3.58- 4.56)	<0.0001
No	1,789 (1.7)	106,643 (98.3)	-	
Gender				
Female	1,133 (2.4)	45,991 (97.6)	1.64 (1.50- 1.78)	<0.0001
Male	987 (1.5)	65,560 (98.5)	-	
Residence				
Urban	1,377 (2.4)	55,350 (97.6)	1.89 (1.72-2.04)	<0.0001
Rural	743 (1.3)	56,201 (98.7)	-	
Origin				
Immigrant	627 (3.5)	17,405 (96.5)	2.27 (2.07- 2.50)	<0.0001
Israel-born	1,493 (1.6)	94,146 (98.4)	-	
No. of siblings				
≤3	1,304 (2.5)	50,756 (97.5)	1.91 (1.75- 2.09)	<0.001
>3	816 (1.3)	60,794 (98.7)	-	
Body mass index				
Normal	1,599 (1.8)	89,444 (98.2)	1	<0.0001
Underweight	100 (2.2)	4,456 (97.8)	1.26 (1.01-1.54)	
Overweight	269 (2.3)	11,481 (97.7)	1.31(1.15-1.49)	
Obese	152 (2.4)	6,170 (97.6)	1.38(1.16- 1.63)	
Population group				
Jews	1,843 (1.8)	97,800 (98.2)	0.93 (0.82-1.06)	0.30
Non- Jews	277 (2.0)	13,751 (98.0)		

Data are presented as n (%)

Table 3. Factors associated with migraine on multivariable analysis

Variable	OR	95% CI	<i>P</i> value
Asthma	1.42	1.19 - 1.68	<0.0001
Allergic rhinitis	3.18	2.80 - 3.63	<0.0001
Female gender	1.58	1.45 - 1.73	<0.0001
Immigrant	1.64	1.47 - 1.82	<0.0001
Obese	1.39	1.17 - 1.64	<0.0001
Overweight	1.26	1.11- 1.44	0.001
≤3 siblings	1.45	1.32 - 1.59	<0.0001
Urban residence	1.75	1.59 - 1.92	<0.0001

OR, odds ratio; CI, confidence interval