

Research Submissions

Association Between Migraine and Atopic Diseases in Childhood: A Potential Protective Role of Anti-Allergic Drugs

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Background.—Migraine is a common cause of headache in childhood. Several studies have investigated the association between migraine and atopic diseases, mostly in the adult population.

Objective.—This study aimed to investigate this association in children.

Methods.—A case-control study was conducted across 3 European tertiary care hospitals between June 2014 and August 2014. Cases ($n = 229$) were children aged 6-18 years consulting for a migraine episode. Controls in the same age range ($n = 406$) were consulting for a minor injury and did not have a history of recurrent headache. Logistic regression analyses tested the effect of atopic diseases and anti-allergic therapies on occurrence of migraine.

Results.—Children with migraine were more likely to have persistent asthma compared to absence of asthma (odds ratio [OR]: 4.57, 95% confidence interval [CI]: 2.04-10.24) and less likely to have been treated by inhaled or nasal corticosteroid (OR: 0.34, 95% CI: 0.15-0.76) or antihistamine therapy (OR: 0.33, 95% CI: 0.18-0.60). The median number of monthly migraine episodes was higher in children with persistent asthma (3; interquartile [IQR]: 1-4; range: 0.5-10) compared to children with intermittent asthma (2; IQR: 1-3; range: 0.1-4) or non-asthmatic children (2; IQR: 1-3; range: 0.1-12) ($P < .01$).

Conclusion.—Persistent childhood asthma was associated with increased risk of migraine and higher frequency of migraine attacks. History of anti-asthmatic or anti-allergic therapies was associated with decreased risk of migraine in children and adolescents. The role of these therapies on the pathogenesis and occurrence of migraine needs to be further elucidated because of the huge potential impact in terms of public health.

Key words: migraine, children, asthma, allergic rhinitis, epidemiology

Abbreviations: CI confidence interval, ED emergency department, ICHD-III International Classification of Headaches Disorders (third edition), IgE immunoglobulin E, IL-1 β interleukin-1 beta, IQR interquartile, LABA long-acting beta2-agonists, OR odds ratio, TNF- α tumor necrosis factor alpha

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INTRODUCTION

Migraine is common in children. Prevalence of migraine in the pediatric population ranges from 3.3% to 21.4%. It is higher in females and increases from childhood to adolescence.^{1,2} Diagnostic criteria for pediatric migraine have been established by the *International Classification of Headaches Disorders* (third edition) (*ICHD-III*).³ The 2 major subtypes of migraine are those with and without aura. Several underlying mechanisms have been postulated such as sterile neurogenic inflammation, arachidonic acid pathway, or serotonin metabolites.⁴⁻⁶

Several studies have documented the association between migraine and various comorbidities or psychosocial factors. In particular, several studies have reported associations between migraine and atopic disease such as food allergy, asthma, or allergic rhinitis.⁷⁻¹⁶ Two population-based studies have suggested a positive association between asthma and migraine in children.^{11,12}

We decided to investigate whether migraine was associated with atopic disease in children presenting to the emergency room. Furthermore, considering that most children with these diseases need preventive therapies for several months during their childhood, we also explored whether these therapies could have an impact on migraine occurrence.

MATERIALS AND METHODS

Enrollment.—We performed a case-control study of consecutive children diagnosed as having migraine across 3 European tertiary care hospitals (Robert Debré, Paris, France; Sacco, Milan, Italy; and Santa Maria della Misericordia, Udine, Italy) between June and August 2014. Written informed consent was obtained from the parents with assent from the children. The study protocol was approved by institutional review boards (IRB) at each center.

Eligibility.—We identified new patients presenting to emergency departments (ED) aged 6-18 years seeking consultation for an episode of

migraine, between June 2014 and August 2014. Controls were composed of children in the same age range, who visited the ED of each participating center for a minor injury in either the upper or the lower extremity, as defined by the Abbreviated Injury Scale,¹⁷ every Monday from 9:00 AM to 5:00 PM. Children with a personal history of migraine or other type of recurrent headache, defined as more than 1 episode of acute headache in the past medical history, were excluded from the control group.

Diagnostic Classification of Migraine.—Pediatric neurologists evaluated every consecutive patient presenting to the ED with headache over the 3-month inclusion period. A structured diagnostic interview verified the diagnosis of migraine according to *ICHD-III* criteria.³ Only children with migraine were included, regardless of the presence of concurrent tension-type headache. Children with other primary headaches were excluded. If children exhibited distinct episodes of migraine with aura or migraine without aura, they were allocated to the migraine with aura subgroup for further analysis.

Diagnostic Classification of Atopic Diseases.—Asthma was defined as a chronic airway inflammatory disorder, characterized by a history of respiratory symptoms such as wheeze, shortness of breath, chest tightness, and cough that vary in intensity and over time, together with a variable expiratory airflow limitation confirmed with either pulmonary function tests or disappearance of cough and wheeze when treated with a beta-agonist during an exacerbation.^{18,19} Children with asthma were classified in intermittent asthma, mild persistent, moderate and severe asthma according to revised 2006 GINA criteria.¹⁸ Allergic rhinitis was defined by association of rhinorrhea, nasal obstruction, nasal itching, and/or sneezing, which is reversible spontaneously or with treatment (nasal steroids or antihistamines) and is characterized by an episodic course, induced after allergen exposure by an immunoglobulin-E(IgE)-mediated inflammation, confirmed by positive allergy testing, either with skin prick tests (IgE-mediated immediate hypersensitivity testing) or allergen-specific serum IgE (sIgE; radioallergosorbant test).^{20,21} Allergic conjunctivitis

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was defined as recurrences of episodic conjunctivitis, associating marked itching and tearing, lid and conjunctival edema/redness, and/or photophobia.^{22,23} Atopic dermatitis was defined as chronic relapsing inflammatory skin disease associated with itching in infancy.²⁴ IgE-mediated food allergy was defined as an adverse health effect arising from a specific immune response that occurred reproducibly on exposure to a given food, including anaphylaxis and cutaneous reactions after food ingestion, and confirmed by positive allergy testing, either with skin prick tests, allergen-specific serum IgE, or oral food challenge.

Data Collection Procedures.—Parent Interview.—Parents were asked to complete a structured questionnaire, which was conducted face to face. The data collected included demographic and medical information, a detailed personal and family history of allergy and atopic disease, including specific queries on all symptoms of atopic disease listed above (See Appendix A). Parents were interviewed together if they were both present at the ED visit. Physicians and parents were informed that the aim of the study was to explore the potential association between migraine and atopic diseases.

Health Booklet and Medical Records Review.—The physicians also examined each child's personal health booklet (carnet de santé [French version]; libretto sanitario [Italian version]). These booklets are mandatory for each child and are given to the parents soon after birth, containing medical data from birth to adulthood. The recorded data include the date of consultation, age, major clinical findings, diagnosis, and therapy. Only physicians may write diagnoses on the health booklet. The booklets also contain medical records from hospital admissions, outpatient consultations, and lab tests. The physicians who participated in the study interviewed parents and children and completed the questionnaire with supplemental information from the booklet and all former medical reports.

Finally, a pediatric consultant classified the atopic disease, as defined above, based on the analyses of the structured questionnaire and all former medical reports, including results of allergy testing and the health booklet.

Collected Data.—The following clinical and biological data were obtained from parental interviews and health booklets for all patients: demographic data (sex, age, consanguinity, pregnancy, gestational age at birth, and birth weight), breastfeeding, diagnosis of migraine in first-degree relatives, diagnosis of atopic disease in first-degree relatives, exposure to passive smoking, coexisting medical conditions, and atopic disease (asthma, allergic rhinitis, allergic conjunctivitis, IgE-mediated food allergy, atopic dermatitis). For children with asthma we recorded anti-asthmatic therapies (inhaled steroids, anti-leukotrienes, long-acting beta2-agonists [LABA], and omalizumab) and pulmonary function tests results, including reversibility of airflow obstruction and methacholine challenge testing. For children with allergic diseases, we recorded any identified allergens and anti-allergic therapies (nasal steroids, antihistamines, and specific immunotherapy). Children were considered to have been treated by anti-asthmatic treatments, nasal steroids, or antihistamines if they had been under these treatments for at least 6 months during their lives or by omalizumab if they had received this at least once. For children with migraine, we also recorded the frequency and characteristics of migrainous episodes, and their treatment.

Statistical Analysis.—We calculated a sample size of 109 patients with 218 in hospital controls. The power calculation showed that the study had 99% power at 5% level of significance to detect an odds ratio (OR) of 4 or more, assuming the percentage of atopic disease in the control group to be at least 5%, as described in a previous retrospective report.¹⁵ Based on the number of migraines diagnosed at each center during a standard month, we estimated a total inclusion period of 3 months. The number of needed controls was calculated on the average number of consultations for minor trauma at the emergency department of each center over the same time period. The primary outcome measure was the presence of migraine. Variables were compared between cases and controls by using the chi-square test or Fisher's exact test for categorical variables and non-parametric test for continuous variables (Mann-Whitney-Wilcoxon). A *P* value of

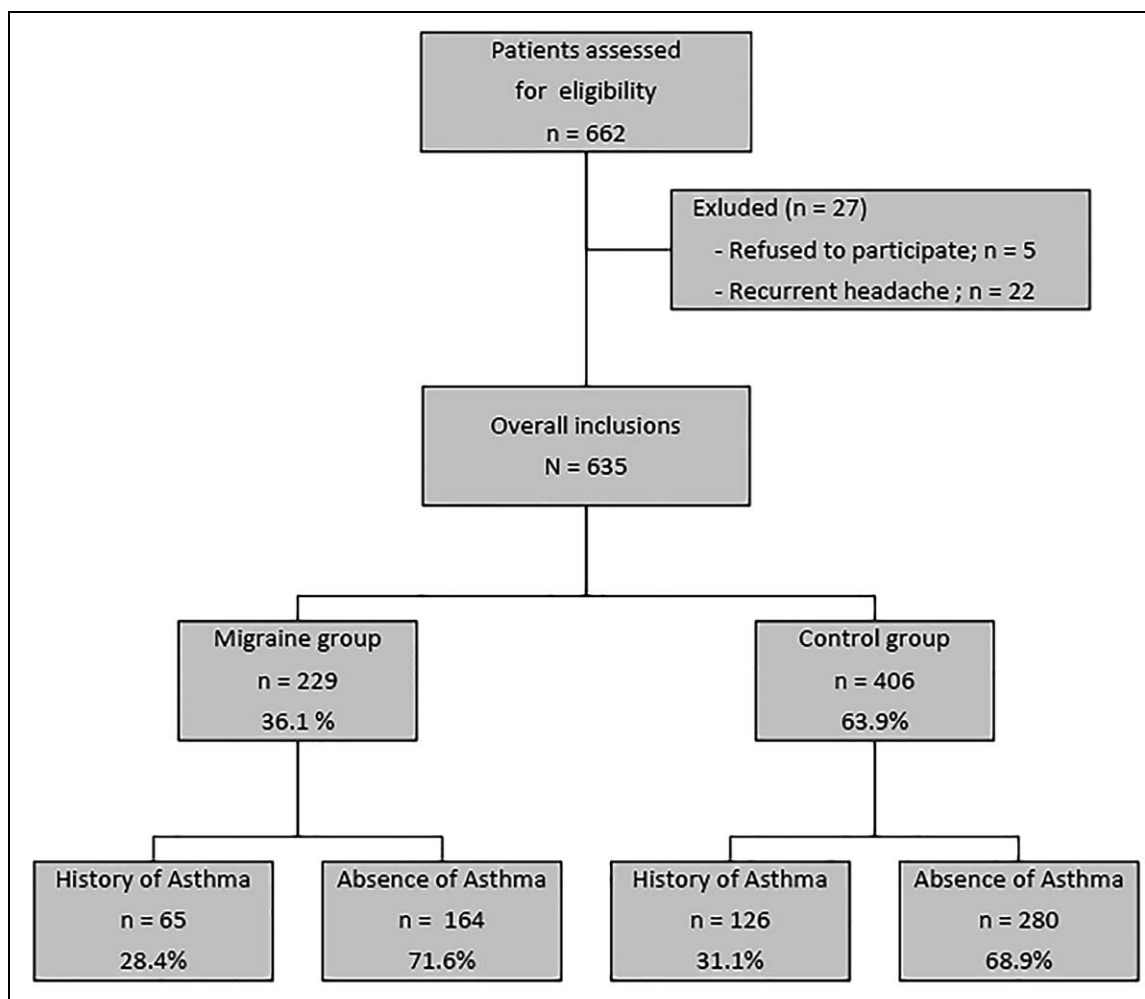


Fig. 1.—Schematic diagram of the participant flow of the study, and prevalence of personal history of asthma, according to migraine or control group.

$<.05$ was considered significant (2-sided). Factors associated with migraine were identified by logistic regression analyses. We selected candidate predictors of migraine based on the results of previous studies, and also tested individual effects of all the different atopic diseases (asthma, allergic rhinitis, allergic conjunctivitis, IgE-mediated food allergy, atopic dermatitis) and anti-allergic therapies. Before including quantitative variable in the model, we assessed that they were linearly related to the log-odds. The initial multivariable model was adjusted for non-collinear covariates associated with a P value $<.20$ in univariate analysis. Only covariates that had a P value $<.05$ were retained in the final model. Interactions

between asthma and treatments and between allergic rhinitis and treatments have been tested. All interactions tested in the model were not significant. Characteristics of the migraine were compared between children with persistent asthma, children with intermittent asthma, or non-asthmatic children using the tests cited above. Statistical analyses were performed using SAS statistical software (version 9.3; SAS Institute, Cary, NC, USA).

RESULTS

A total of 229 patients with migraine (36.1%), of which 147 presented without aura and 82 with aura, and 406 controls were included in the study (Fig. 1). Only 2 families in the migraine group and

Table 1.—Characteristics of Children Included in the Study, According to Migraine or Control Group

Characteristics	Migraine Group N = 229	Control Group N = 406	P Value
Males, No. (%)	108 (47.2)	249 (61.3)	<.001
Age at evaluation, median (IQR), years	11.8 (8.7; 13.4)	10.3 (8.0; 12.5)	<.001
Gestational age at birth, weeks			
Median (IQR)	40 (38; 40)	39 (38; 40)	.060
Minimum; maximum	27; 41	28; 42	
Missing data	N = 1	N = 4	
Prematurity (gestational age at birth <37 weeks), n (%)	26 (11.4)	24 (6.0)	.015
Missing data	N = 1	N = 4	
Birth weight, g			
Median (IQR)	3255 (2890; 3600)	3340 (3000; 3660)	.011
Minimum; maximum	900; 4640	1180; 5200	
Missing data	N = 1	N = 3	
Birth weight, SDS			
Median (IQR)	0.11 (−0.53; 0.65)	0.15 (−0.61; 0.80)	.49
Minimum; maximum	−4.64; 5.24	−3.19; 4.25	
Missing data	N = 1	N = 4	
Exclusive breastfeeding, n (%)	145 (63.3)	220 (54.3)	.028
Missing data	N = 0	N = 1	
Exposure to passive smoking at home, n (%)	54 (23.6)	100 (24.6)	.77
Family history			
Parental consanguinity, n (%)	9 (3.9)	18 (4.4)	.76
Migraine, n (%)	161 (70.3)	168 (41.4)	<.001
Atopic diseases, n (%)	109 (47.6)	230 (56.7)	.031

IQR, interquartile range. Data are reported as No (%) of participants unless otherwise indicated.

3 families in the control group refused to provide consent. Twenty-two children (9.6%) were excluded from the control group because of recurrent headaches. Baseline characteristics of patients are shown in Table 1.

Characteristics of headaches in children diagnosed with migraine are presented in Table 2.

Personal history of any atopic disease was scored in 57.6% of children diagnosed with migraine (132/229) and in 67.2% of children in the control group (273/406), as detailed in the Table 3.

The multivariable logistic regression results are presented in Table 4 and found that variables independently associated with migraine were female gender, age at evaluation, prematurity, exclusive breast feeding, family history of migraine, history of asthma, and absence of treatment by inhaled or nasal corticosteroid, or antihistamine therapy.

Persistent asthma was associated with increased risk of migraine compared to absence of asthma (odds ratio [OR]: 4.57, 95% confidence interval [CI]: 2.04-10.24). The subgroup analysis confirmed those results in migraine with aura (OR: 4.46, 95% CI: 1.21-16.47) and in migraine without aura (OR: 5.23, 95% CI: 2.14-12.79).

Children with migraine were less likely to have been treated by inhaled or nasal corticosteroid (OR: 0.34, 95% CI: 0.15-0.76) or antihistamine therapy (OR: 0.33, 95% CI: 0.18-0.60). The subgroup analysis for migraine subtypes confirmed negative association between migraine with aura and antihistamine therapy (OR: 0.32, 95% CI: 0.14-0.71), and between migraine without aura and inhaled or nasal corticosteroid (OR: 0.28, 95% CI: 0.11-0.70) and antihistamine therapy (OR: 0.36, 95% CI: 0.18-0.73).

The subgroup analysis for classes of age confirmed some of the previous results: in children

Table 2.—Headache and Associated Symptoms in Patients With Pediatric Migraine

Characteristics	Migraine Group N = 229
Age at first manifestation of headache, median (IQR), years	7.0 (5.0; 11.0)
Time since first manifestation of headache, median (IQR), years	3.1 (1.7; 4.7)
Migraine attacks per month, median (IQR), No.	2.0 (1.0; 3.0)
Episodic migraine	218 (95.2%)
Aura	82 (35.8)
Visual symptoms	57 (69.5)
Sensory symptoms	18 (22.0)
Motor symptoms	7 (8.5)
Prescription of preventive therapy	23 (10.0)
Pain during migraine attacks reported	
Unilateral location	90 (39.3)
Pulsating quality	158 (69.0)
Aggravation by or causing avoidance of routine physical activity	199 (86.9)
Nausea	153 (66.8)
Vomiting	94 (41.1)
Phonophobia	178 (77.7)
Photophobia	180 (78.6)

IQR, interquartile range. Data are reported as No (%) of participants unless otherwise indicated.

aged 6-12 years, migraine was associated with persistent asthma (OR: 6.63, 95% CI: 2.33-18.90), inhaled or nasal corticosteroid (OR: 0.33, 95% CI: 0.12-0.94) and antihistamine

therapy (OR: 0.31, 95% CI: 0.13-0.73); in children aged 12-18 years, migraine was associated with antihistamine therapy (OR: 0.93, 95% CI: 0.19-0.79).

Table 3.—Distribution of Atopic Diseases in Children Included in the Study, According to Migraine or Control Group

Characteristics	Migraine Group N = 229	Control Group N = 406	P Value
Conditions reported in infancy and childhood, No. (%)			
IgE mediated food allergy	17 (7.4)	36 (8.9)	.53
Atopic dermatitis	40 (17.5)	92 (22.7)	.12
Allergic rhinitis	40 (17.5)	103 (25.4)	.02
Allergic conjunctivitis	32 (14.0)	92 (22.7)	.01
Asthma			
- Mild, moderate, or severe persistent	57 (24.9)	75 (18.5)	<.001
- Intermittent	8 (3.5)	51 (12.6)	
- Absence	164 (71.6)	280 (68.9)	
Treatments			
Inhaled corticosteroid	42 (18.3)	100 (24.6)	.07
Long-acting beta2 agonist	31 (13.5)	58 (14.3)	.90
Nasal corticosteroid	8 (3.5)	46 (11.3)	<.001
Nasal or inhaled corticosteroid	43 (18.8)	112 (27.6)	.02
Antihistamine therapy	26 (11.4)	108 (26.6)	<.001
Leukotriene modifiers	7 (3.1)	24 (5.9)	.11

Table 4.—Univariate and Multivariable Odds Ratios of Migraine by Demographic Characteristics and Atopical Diseases (n = 629)

Factors	Univariate analysis		Multivariate analysis	
	Crude OR [95% CI] Migraine	P Value	Adjusted OR [95% CI] Migraine	P Value
Girls (vs boys)	1.78 [1.28-2.46]	<.001	1.78 [1.24-2.58]	<.01
Age at evaluation (per 1 year)	1.12 [1.06-1.18]	<.001	1.15 [1.08-1.22]	<.001
Prematurity†	2.03 [1.13-3.62]	.02	2.31 [1.20-4.44]	.01
Exclusive breast feeding	1.45 [1.04-2.02]	.03	1.80 [1.24-2.62]	<.01
Family history of migraine	3.35 [2.37-4.74]	<.001	2.96 [2.04-4.30]	<.001
Personal history of:				
<i>IgE-mediated food allergy</i>	0.82 [0.45-1.50]	.53		
Allergic conjunctivitis	0.56 [0.36-0.86]	<.01		
Allergic rhinitis	0.62 [0.41-0.94]	.02		
Atopic dermatitis	0.72 [0.48-1.09]	.12		
Asthma				
<i>Intermittent</i>	0.27 [0.12-0.58]	<.01	1.25 [0.47-3.23]	.65
<i>Mild, moderate, or severe persistent</i>	1.30 [0.87-1.93]	.20	4.57 [2.04-10.24]	<.001
Absence	1		1	
Treatments (reference is absence)				
Long-acting beta2 agonist	1.07 [0.59; 1.95]	.83		
Nasal or inhaled corticosteroid	0.61 [0.41-0.90]	.01	0.34 [0.15-0.76]	<.01
Antihistamine therapy	0.35 [0.22-0.56]	<.01	0.33 [0.18-0.60]	<.001
Leukotriene modifiers	0.51 [0.21; 1.26]	.15		

OR, odds ratio; 95% CI, 95% confidence interval. †Prematurity: gestational age at birth <37 weeks.

To investigate the large variation between unadjusted and adjusted OR (Table 4), we performed a description of the prevalence of atopic diseases in children diagnosed with migraine and in controls, stratified for the presence or absence inhaled or nasal corticosteroid (Appendix B). This analysis supports that the association between migraine and asthma, allergic rhinitis, or allergic conjunctivitis was confounded by treatments.

When considering migraine characteristics, we found that the median number of monthly migraine episodes was higher in children with persistent asthma (3; interquartile [IQR]: 1-4; range: 0.5-10) compared to children with intermittent asthma (2; IQR: 1-3; range: 0.1-4) or non-asthmatic children (2; IQR: 1-3; range: 0.1-12) ($P < .01$). Migraine pain aggravation by physical activity was more frequently scored in children with persistent asthma

(98.3%) compared to children with intermittent asthma (87.5%) or non-asthmatic children (82.9%) ($P < .01$).

DISCUSSION

We aimed to investigate the possible association of atopic diseases with pediatric migraine, and the potential role of preventive treatments. We show for the first time an increased risk of migraine in children with persistent asthma and a decreased risk of migraine in children treated by long-term local corticosteroid or antihistamine therapies.

There are several reports of an association between asthma or atopic disorders and migraine, mostly in adults,^{7-10,13,16} but also in children.^{11,12,14,15,25-29} Authors have raised several allergic and non-allergic hypotheses to explain this association. First, allergens may lead to an

activation of trigeminal afferents through inflammatory mediators, particularly degranulation of dural mast cells.^{30–32} Conversely, the association between asthma and migraine could be independent from atopic mechanisms, involving inflammatory mediators such as tumor necrosis factor alpha (TNF- α) and interleukin-1 beta (IL-1 β).^{33,34} Finally, a hypothesis of migraine as a potential side effect of allergy or asthma treatment has been discussed, but no clear-cut evidence of an association exists.^{35,36}

We found a positive association between persistent asthma and migraine and an increased frequency of migrainous episodes in those asthmatic children. This association of asthma and migraine in our series was independent of the presence of anti-allergic treatment. Prior studies have described the association between migraine and asthma in children,^{15,25,29} adolescents,¹¹ and adults.^{7,8} Some authors have found this association stronger in patients without allergic rhinitis^{8,16} speculating that the link between asthma and migraine may at least in part be independent of the allergic mechanisms described above. In this case, either inflammatory mediators such as TNF- α and IL-1 β or functional abnormalities in smooth muscle of both cerebral blood vessels and airways could be considered.^{33,34}

In a univariate analysis, we also found a negative association between allergic rhinitis or conjunctivitis and migraine. This is inconsistent with previous studies that found a positive association in adults¹⁰ or children.^{11,12,14,15,37} Previous studies in children presented methodological limitations that may have biased the conclusions, in particular variability in the diagnosis of allergic rhinitis^{11,12,14} and possible recall bias. Moreover, some of those studies did not analyze the effect of treatments and potential confounding factors.^{14,37} After adjustment for confounding factors and treatments, this association was not persisting. Two hypotheses must be raised. First, a true negative association between migraine and allergic rhinitis or conjunctivitis may have been hidden by under-reporting of allergic diseases. This hypothesis is inconsistent with previous studies which found a positive association, but has

to be investigated by further research. We can also hypothesize that allergic rhinitis and conjunctivitis act as confounding factors and that this univariate association was in fact due to negative association between migraine and antihistamine therapy or nasal or inhaled corticosteroid. To our knowledge, no previous study has found such an association. Some authors have found that plasma histamine levels are chronically elevated in migraineurs.³⁸ Other authors have suggested that the association of atopic diseases and migraine might be due to sterile neurogenic inflammation⁴ or that administration of immunotherapy might be associated with a decreased prevalence, frequency, and disability of migraine headache in adults aged 18–40 years.³¹ Investigators have speculated that inflammatory mediators released by mast cells during the allergic response may trigger migraine through the activation of trigeminal afferents.^{5,30–32,39} Prostaglandin and leukotriene released by monocytes, macrophages, and mast cells have been found in higher levels in children with migraine,⁴ and a decrease of these eicosanoids in patients with anti-allergic therapies or corticosteroid may explain the negative association between migraine and those treatments.^{40–43} We therefore hypothesize that antihistamine therapies may decrease histamine levels and inflammatory response, as has been suggested in previous *in vitro* studies.^{44,45} Nonetheless, another hypothesis might be that migraineurs may have had side effects to antihistamine therapies and been less likely to use them, resulting in a bias in estimation of the association.

Our study has some limitations, most of which are due to the inherent weaknesses associated with case-control studies vs prospective longitudinal studies. However, a prospective longitudinal study, from birth until adolescence, seemed difficult to perform. To serve as a proof of concept, we preferred to perform a multicenter study that included a sufficient number of patients to increase the generalizability of our findings. Moreover, we performed the study in 2 European countries to include a sufficient number of patients and to allow increased generalizability of our results. Furthermore, the association between pediatric migraine

and classical risk factors such as gender and family history of migraine is an argument to assess the external validity of our study. Second, we cannot exclude a recall bias for the atopic diseases. The possibility of a recall bias for an event many years previous is possible. However, the parental interview was completed by a review of personal medical records. Furthermore, parents vividly remembered the episodes of atopic diseases, because of their recurrence and eventual treatment. Finally, we focused on children consulting for migraine at the ED between June and August, who might not be representative of all children with migraine occurring throughout the year. It is possible that children with milder or less recurrent headaches do not consult to the ED but rather their family doctor. It is also possible that there may be a seasonal element. Studies covering the 4 seasons have to be planned to address this potential issue and to increase the generalizability of our findings. At last, we only investigated the association between migraine and allergic rhinitis, so additional studies have to study the association between migraine and non-allergic rhinitis (eg, vasomotor rhinitis).

In conclusion, we found a higher risk of migraine and a higher frequency of migrainous episodes in children with persistent asthma, and a lower risk of migraine in children treated by long-term nasal or inhaled corticosteroid or antihistamine therapies. Association between asthma and migraine has to be confirmed by supplemental studies such as case control studies comparing prevalence of migraine in subjects with or without asthma. We also found a lower risk of migraine in children with anti-allergic therapies. Additional longitudinal studies in young children are required to discriminate between a hypothesis of a preventive role of anti-allergic therapies in the occurrence of migraine, by acting on inflammatory mediators released by mast cells during the allergic response, and a hypothesis of negative association between

allergic rhinitis and migraine. From a more clinical point of view, management of children with migraine should also include screening for associated asthma and allergic symptoms.

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Appendix A: Administered Questionnaire on Atopical Diseases

1. Asthma History

History of respiratory symptoms

- Has a doctor ever diagnosed that your child has asthma?
- Does the child have wheeze, shortness of breath, chest tightness cough, dyspnea and/or heavy breathing during day?
- How often does the child have cough, wheeze, dyspnea or heavy breathing (number of times per week or day)? What triggers the symptoms? How are they handled?
- During nights, does the child have cough and/or awakenings? Does he have tiredness during the day?
- How long has he had these day and night symptoms?
- Does the child have these symptoms all the time or do they come and go?
- Does the child have shortness of breath or cough during physical activity?

Level of asthma symptom control

- In the past 4 weeks, has the child had:
- Daytime asthma symptoms (cough, wheeze, dyspnea or heavy breathing) more than twice/week?
- Any night waking due to asthma?
- Reliever needed for symptoms more than twice/week?
- Any activity limitation due to asthma?

Reliever use

- How often is reliever medication used?
- Pre-exercise use (sports)
- Use for relief of symptoms

Others treatments

- History of treatment by inhaled steroids? If yes, duration of this treatment?
- History of treatment by anti-leukotrienes? If yes, duration of this treatment?
- History of treatment by long-acting beta2-agonists (LABA)? If yes, duration of this treatment?
- History of treatment by long-acting beta2-agonists omalizumab? If yes, duration of this treatment?

Response treatment

- Does the cough and wheeze disappear when treated with a beta-agonist during an exacerbation?

Lung function

- Date. Curves and technique. Obstructive syndrome. Bronchodilator reversibility. Methacholine challenge testing

2. Allergic Rhinitis and Allergic Conjunctivitis History

History of allergic symptoms

- Has a doctor ever diagnosed that your child has hay fever or allergic rhinitis?
- Does the child have rhinorrhoea, nasal itching, sneezing, nasal congestion and/or obstruction?
- Does the child have eye symptoms? Does the child have watery or itchy eyes?
- Does the child have recurrences of episodic conjunctivitis, associating marked itching and tearing, lid and conjunctival edema/redness and/or photophobia?
- How long has he had these symptoms? Are those symptoms seasonal or year-round?
- Does the child have the symptoms all the time or do they come and go?
- Are you aware of anything that seems to bring the symptoms on, such as being outdoors, around animals or related to something you handle at work or at home?

Treatment

- What medications have you already tried for these symptoms?
- What medications are being taken for nasal symptoms?
- What medications are being taken for eye symptoms?

3. Atopic Dermatitis History

- Does the child have chronic relapsing inflammatory skin disease associated with itching?
- Has a doctor ever diagnosed that your child has eczema (atopic dermatitis)?
- How long has he had these symptoms?
- Has the child ever been treated by topical corticosteroids?

4. Food Allergy History

- Has a doctor ever diagnosed that your child has a food allergy?
- Does the child have adverse health effect that occurred reproducibly on exposure to a given food?
- Does the child have cutaneous reactions that occurred reproducibly after a given food?
- Does the child have vomiting, throat or tongue swelling, shortness of breath and/or lightheadedness that occurred reproducibly after a given food?
- If yes to one of these questions, please specify which food.

5. Allergy Testing

- Allergen-specific serum IgE (sIgE; radioallergosorbant test): date; results
- Skin prick tests (IgE-mediated immediate hypersensitivity testing): date; results
- Oral food challenge: date; results

6. Anti-Allergic Therapies

- History of treatment by nasal steroids? If yes, duration of this treatment?
 - History of treatment by antihistamines? If yes, duration of this treatment?
 - History of treatment by specific immunotherapy? If yes, duration of this treatment?
-

Appendix B: Distribution of Atopic Allergic Rhinitis and Conjunctivitis and Asthma in Children Included in the Study, According to Migraine or Control Group, Stratified for Absence or Presence of Corticosteroid

	Nasal or Inhaled Corticosteroid n = 155		Absence of Nasal or Inhaled Corticosteroid n = 480	
	Migraine Group n = 43	Control Group n = 112	Migraine Group n = 186	Control Group n = 294
Conditions reported in infancy and childhood, No. (%)				
Allergic rhinitis	24 (55.8)	69 (61.6)	16 (8.6)	34 (11.6)
Allergic conjunctivitis	15 (34.9)	53 (47.3)	17 (9.1)	39 (13.3)
Asthma				
- Mild, moderate, or severe persistent	36 (83.7)	69 (61.6)	21 (11.3)	6 (2.0)
- Intermittent	6 (14.0)	36 (32.1)	2 (1.1)	15 (5.1)
- Absence	1 (2.3)	7 (6.3)	163 (87.6)	273 (92.9)

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