Children with allergic diseases have an increased subsequent risk of migraine upon reaching school age

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ABSTRACT

The association between migraine and allergy has remained a subject of debate for more than a century. To systemically investigate the interaction between children with antecedent allergic diseases and their future risks of migraine on reaching school age, we recruited 16,130 children aged 7–18 with migraine diagnosed between 2000 and 2008, and 64,520 matched controls without a history of migraine. The ORs of migraine were calculated for the association with allergic diseases diagnosed before migraine diagnosis. The allergic diseases included atopic dermatitis, allergic conjunctivitis, allergic rhinitis (AR), and asthma. Children with preceding allergic diseases had a greater subsequent risk of migraine than the controls. Among the four evaluated diseases, AR had the highest adjusted OR (aOR) of 2.17 (95% CI 2.09 to 2.26). Children with all four allergic diseases had the highest aOR of 3.59 (95% CI 2.91 to 4.44). Further, an increasing trend of aORs was observed with more allergic disease-associated medical consulting. Our study indicates that children with allergic diseases are at increased subsequent risk of migraine when they reach school age, and the risk shows a cumulative effect of more allergic diseases and more allergy-related healthcare.

Significance of this study

What is already known about this subject?
- Migraine is the most prevalent type of primary headache in children.
- Childhood migraine may persist into adulthood.
- The etiology of migraine is not fully clear.
- The relationship between migraine and allergy has remained a subject of debate for more than a century.

What are the new findings?
- Children have more concurrent allergic diseases at greater subsequent risk of migraine on reaching school age.
- Among the four evaluated diseases, children with allergic rhinitis had the highest risk for migraine.
- The subsequent risk of migraine was associated with a cumulative effect of concurrent allergic diseases and allergic disease-related health utilization.

How might these results change the focus of research or clinical practice?
- Clinicians should be aware of the diagnosis of migraine in children with atopy and complaints of chronic and relapsing headache.
- Early intervention to prevent and treat allergic diseases and subsequent risk of migraine needs more research in the future.

INTRODUCTION

Migraine is the most prevalent type of primary headache in children.[1] The chronic relapsing and disabling nature of childhood migraine greatly impacts school performance and quality of life of affected children.[1 2] Besides, childhood migraine may continue into adulthood.[2] To date, the exact pathogenesis of migraine is unclear. Migraine has been considered a neurovascular pain syndrome[3 4] associated with vasoactive neuropeptide-induced neurovascular phenomena,[3 4] abnormal cortical excitation and inhibition,[4–6] trigeminovascular system sensitization and activation,[7] and neurogenic inflammation.[8 9] The possible link between migraine and allergy has remained a subject of debate for more than a century.[10] In 1927, Vaughan[11] initially reported that migraine was triggered by food allergy in 10 patients whose conditions were improved with specific food avoidance. In 1952, Unger and Unger[12] reported that more than half of all migraine sufferers had a personal and family history of allergic disease. The patients' migraine headaches were relieved with diets that avoided specific trigger foods, such as milk, chocolate, or wheat.[12] In 1965, Shapiro and Eisenberg reported a case series study of 100 patients with migraine who had been diagnosed with allergy; in most patients, migraine headaches improved after immunotherapy or food avoidance.[13] Since 1990, evidence about the high prevalence of migraine in patients with allergic diseases has accumulated as a result of some case–control studies.[14–16] However, most of these were hospital-based studies with limited numbers of cases that mainly focused on adults with migraine. More recently,

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several studies showed increased levels of allergy-related proinflammatory mediators, such as prostaglandin F2a (PGF2a) and cysteinyl leukotrienes, during attacks of migraine headache.[8 17 18] Despite historical interest,[12 19–21] no large-population epidemiologic study systemically has evaluated the interaction between allergic diseases and the subsequent risk of migraine in children. An understanding of the interaction between migraine and allergic disease will help clinicians to develop effective strategies to prevent migraine and combat migraine-associated disabilities and healthcare burden. Thus, we performed a nationwide case–control study to investigate children with allergic diseases, including allergic conjunctivitis (AC), allergic rhinitis (AR), asthma, and atopic dermatitis (AD), and their future risk of migraine.

METHODS

Data sources

Taiwan launched the single-payer compulsory National Health Insurance (NHI) program at the beginning of 1995, and this program covers almost all citizens with modest cost sharing.[22] All health claims data are collected in the NHI Research Database (NHIRD) and managed by the NHI program (http://www.nhi.gov.tw/english/index.aspx).[22–24] The children's file (age at <18 years), derived from the NHIRD, contains a randomly selected sample of half population of Taiwan children.[24–27] The disease was coded based on the International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM). Identities of the insured were encrypted, and all data were analyzed anonymously to comply with the Personal Information Protection Act. All methods were performed in accordance with the relevant guidelines. The disease was coded based on the ICD-9-CM.

Study subjects

We recruited children aged 7–18 years with migraine diagnosed in 2000–2008. They composed the migraine group and the migraine diagnosis date as the index date. Children with migraine were defined as those with at least two claims coded in the primary diagnosis field at the inpatient or ambulatory claim for migraine. Children aged under 7 years or more than 18 years and with incomplete information on demographics were excluded. The index date for the control patients was randomly appointed a month and day with the same index year of the matched migraine cases. For each migraine patient, four controls with no history of migraine were matched by age (within 1-year intervals), sex, urbanization level, and year of migraine diagnosis (index year).

Definition of variables and comorbidity

We grouped the urbanization level into seven levels based on Liu's report.[23] Level 1 was the highest urbanization and level 7 the lowest. Because there were few children in levels 5–7, we combined them into level 4. The diagnoses of AC (ICD-9 codes: 372.05, 372.10, and 372.14), AR (ICD-9 code: 477), asthma (ICD-9 codes: 493 and 494), and AD (ICD-9 code: 691) only before the diagnosis of migraine (index date) were identified. Only those individuals having at least three consecutive corresponding diagnoses by physicians were designated as having allergic disorders.

Hence, the diagnoses of allergic diseases were made in earlier years before migraine was diagnosed, not limited to 2000–2008.

Statistical analysis

The distributions of the comparison controls and migraine cases were exhibited as the mean and SD for continuous variables and the number and percentage of each category variable. To test the differences between the two groups, we applied t-test for continuous variables and χ^2 test for categorical variables. Multivariate logistic regression models were used to calculate the ORs and 95% CIs for the interaction of earlier allergic diseases and subsequent migraine. We used SAS V.9.3 software to manage and analyze the data, and $p<0.05$ was considered as statistically significant.

RESULTS

We determined the annual incidence rate of migraine among children aged 7–18 years. The mean annual incidence rate from 2000 to 2008 was 6.54 (range: 5.71–7.45) per 10,000 children. Regarding the migraine subtype, 70.1% of patients with migraine were coded as having unspecified migraine, whereas 9.1% of cases experienced migraine with aura. A total of 16,130 children with migraine were identified, including 6223 boys (38.6%) and 9907 girls (61.4%). The mean (SD) age at migraine diagnosis was 13.6 (3.15) years. The occurrence rates of all allergic diseases before index date were greater in children with migraine than in the non-migraine children: AC (20.6% vs 14.1%, p<0.001), AR (31.9% vs 17.7%, p<0.001), asthma (11.5% vs 6.9%, p<0.001), and AD (3.6% vs 2.1%, p<0.001) (table 1).

In the overall study population, the greatest subsequent risk of migraine was observed in children with AR, with an adjusted OR (aOR) of 2.17 (95% CI 2.09 to 2.26), followed by asthma, with an aOR of 1.76 (95% CI 1.66 to 1.87); AD, with an aOR of 1.74 (95% CI 1.58 to 1.93); and AC, with an aOR of 1.58 (95% CI 1.52 to 1.66). Boys with allergic disease had a greater subsequent risk of migraine than girls, with aORs of 2.21 for AR (95% CI 2.08 to 2.35), 1.83 for asthma (95% CI 1.69 to 1.98), 1.80 for AD (95% CI 1.56 to 2.09), and 1.61 for AC (95% CI 1.50 to 1.72). The aORs of subsequent migraine increased along with the concurrent number of allergic diseases (table 2). In multivariate logistic regression analysis, the aOR increased with the number of preceding allergic diseases from 1.78 (95% CI 1.71 to 1.86) for those with only one allergic disease to 2.33 (95% CI 2.22 to 2.45) for those with at least two allergic diseases (p value for trend <0.001; table 2). We subsequently analyzed the joint effects of multiple allergic diseases and interaction of subsequent migraine by multivariate logistic regression analysis and observed the greatest aORs in children with all four allergic diseases (3.59, 95% CI 2.91 to 4.44). Among these children, the aOR increased further to 3.39 (95% CI 2.47 to 4.66) in girls but decreased to 3.77 (95% CI 2.85 to 4.99) in boys (table 2). In addition, we analyzed the association between the annual frequency of allergic disease-associated medical consulting and the occurrence of migraine on school age. Compared with those without allergic diseases, the aORs were greater for children requiring more allergic disease-associated medical consulting (table 3).

Table 1 Comparison of sociodemographic factors and comorbidities between school-aged children with and without migraine

	Total N=80,650	Non-migraine N=64,520	Migraine N=16,130	
	n (%)	n (%)	n (%)	P values
Age (year), mean±SD*	13.6±3.15	13.6±3.16	13.6±3.15	0.93
Stratified age				0.99
6–12	23,705 (29.4)	18,964 (29.4)	4741 (29.4)	
13–18	56,945 (70.6)	45,556 (70.6)	11,389 (70.6)	
Sex				0.99
Girls	49,535 (61.4)	39,628 (61.4)	9907 (61.4)	
Boys	31,115 (38.6)	24,892 (38.6)	6223 (38.6)	
Urbanization†				0.99
1 (highest)	22,050 (27.3)	17,640 (27.3)	4410 (27.3)	
2	24,280 (30.1)	19,424 (30.1)	4856 (30.1)	
3	13,995 (17.4)	11,196 (17.4)	2799 (17.4)	
4 (lowest)	20,325 (25.2)	16,260 (25.2)	4065 (25.2)	
Comorbidity				
Allergic conjunctivitis	12,414 (15.4)	9088 (14.1)	3326 (20.6)	<0.001
Allergic rhinitis	16,594 (20.6)	11,445 (17.7)	5149 (31.9)	<0.001
Asthma	6292 (7.8)	4436 (6.9)	1856 (11.5)	0.001
Atopic dermatitis	1951 (2.4)	1365 (2.1)	586 (3.6)	<0.001

χ^2 test.
*t-test.
†The urbanization level was categorized by the population density of the residential area into four levels, with level 1 as the most urbanized and level 4 as the least urbanized.

DISCUSSION

This is one of the few studies that systemically evaluated the association between antecedent allergic diseases and the subsequent risk of migraine in a large population of children. In the current analysis based on medical claims analysis, we found a positive association between allergic diseases and migraine in children. Compared with previous studies,[3–16] we investigated the effects of a specific type of allergic disease and the several common allergic diseases; the onset of migraine after allergic diseases and the cumulative effects of concurrent allergic diseases were investigated to determine the possible causal relationships. In addition, this study found a consistent association between all investigated allergic diseases, including AR, AD, AC, and asthma, and the related risk of migraine. Among the four evaluated allergic diseases, AR presented the greatest risk of subsequent migraine; patients with AR had a 117% increased risk of subsequent migraine. Furthermore, the risk of migraine increased with the number of concurrent allergic diseases and the frequency of medical visits for allergic diseases, indicating that a larger burden of clinically apparent allergic symptoms was associated with a higher prevalence of migraine.

Migraine was ranked by the WHO as the 19th disabling disease causing great health and economic burden. However, studies estimating the incidence of childhood migraine with

Table 2 Association between independent and joint effects of allergic diseases and risk of migraine

	All (N=80,650)	Girls (n=49,535)	Boys (n=31,115)
	OR (95% CI)	OR (95% CI)	OR (95% CI)
Allergic diseases			
Allergic conjunctivitis (AC)	1.58 (1.52 to 1.66)*	1.57 (1.48 to 1.66)*	1.61 (1.50 to 1.72)*
Allergic rhinitis (AR)	2.17 (2.09 to 2.26)*	2.19 (2.08 to 2.30)*	2.21 (2.08 to 2.35)*
Asthma	1.76 (1.66 to 1.87)*	1.71 (1.57 to 1.86)*	1.83 (1.69 to 1.98)*
Atopic dermatitis (AD)	1.74 (1.58 to 1.93)*	1.70 (1.48 to 1.94)*	1.80 (1.56 to 2.09)*
AC and AR	2.16 (2.03 to 2.29)*	2.20 (2.03 to 2.40)*	2.12 (1.95 to 2.31)*
AC, AR and asthma	2.28 (2.07 to 2.51)*	2.23 (1.92 to 2.58)*	2.34 (2.05 to 2.66)*
AC, AR and AD	2.97 (2.52 to 3.51)*	2.94 (2.30 to 3.76)*	3.00 (2.40 to 3.76)*
AC, AR and asthma, AD	3.59 (2.91 to 4.44)*	3.39 (2.47 to 4.66)*	3.77 (2.85 to 4.99)*
Number of concurrent allergic disease			
0	1.00 (reference)	1.00 (reference)	1.00 (reference)
1	1.78 (1.71 to 1.86)*	1.76 (1.67 to 1.86)*	1.84 (1.72 to 1.96)*
2+	2.33 (2.22 to 2.45)*	2.30 (2.15 to 2.47)*	2.42 (2.25 to 2.60)*
P for trend	<0.001	<0.001	<0.001

*P<0.001.

Table 3 Association between frequency of annual medical visit due to allergic disease and subsequent risks of migraine

Frequency, visit per year	None	1–2	>2	
Allergic diseases	**OR (95% CI)**	**OR (95% CI)**	**OR (95% CI)**	**P values for trend**
Allergic conjunctivitis	1.00 (reference)	1.54 (1.46 to 1.62)*	1.67 (1.56 to 1.80)*	<0.001
Allergic rhinitis	1.00 (reference)	1.78 (1.69 to 1.87)*	2.71 (2.57 to 2.85)*	<0.001
Asthma	1.00 (reference)	1.60 (1.48 to 1.73)*	1.98 (1.83 to 2.15)*	<0.001
Atopic dermatitis	1.00 (reference)	1.60 (1.42 to 1.81)*	2.07 (1.75 to 2.44)*	<0.001

*P<0.001.

a large population have been very limited. In this study, the mean annual incidence rate of migraine among children aged 7–18 years was 6.54 per 10,000 children. From patients with migraine, 70.6% experienced migraine onset from 13 to 18 years of age, and 38.6% of school-aged migraine cases affected boys. Our results revealed that school-aged boys with allergic diseases had a higher risk of migraine than did girls. Previous epidemiologic studies reported a higher frequency of childhood migraine among boys than girls before puberty, whereas migraine was more prevalent among girls after puberty and in adulthood.[2 10 11] This earlier age of onset explains why boys with allergic diseases have a higher risk of migraine relative to girls. Moreover, children with migraine more frequently lived in urban areas and this finding had not previously been identified.

Our study found that children with allergic diseases have a greater subsequent risk of developing migraine later in life. Healthcare providers should be alert to the migraine in children with allergic diathesis and a recurrent headache. During brain development, changes in the organization of structural brain networks are crucial, as the nervous system may respond differently to external stimuli and/or disease (eg, migraine).[28] Earlier allergic disorders might affect neural network functioning and stability during brain development, which might be important in the pathophysiology of migraine during early childhood.

Although the exact pathophysiology of migraine remains to be elucidated, sterile neuroinflammation is thought to play an crucial role in migraine attack.[7 18 29–31] Several studies reported increased levels of proinflammatory cytokines, such as interleukin-1a, soluble tumor necrosis factor receptor-1, and tumor necrosis factor-a, in the serum of patients during their migraine attack.[11 29 32] Ince *et al* found that leukotriene E4 (LT-E4) and PGF2a levels were significantly higher in the urine and blood of children with migraine during headache periods relative to non-headache periods.[17] The elevation in plasma and urine concentrations of LT-E4 have been similarly noted in patients with allergic diseases such as asthma, AR, and AD.[33] Prostaglandins are arachidonic acid metabolites synthesized by stimulated mast cells via the cyclooxygenase pathway. PGF2a is excreted in large amounts in the urine and may be a surrogate marker of mast cell activation and PG synthesis. Additionally, plasma PGF2a concentrations increase during inflammatory responses, suggesting that PGF2a is a reliable marker of inflammation.[30] The elevated levels of these inflammatory mediators were compatible with the hypothesis linking neuroinflammation in trigeminal vascular blood vessels with migraine pathophysiology.

This study has several limitations. Although we adjusted for several potential confounders in the statistical analysis, several possible confounding variables associated with migraine, including family history of migraine, dietary habits, physical activity, occupational exposures, family member's smoking habits, stress, and emotional factors, were not included in our database.[34 35] Besides, detailed information and laboratory data related to allergy, including serum IgE levels, eosinophil levels, skin prick tests, and family histories of atopy, were also unavailable in the database. The prevalence of migraine might be underestimated because children with less severe or less frequent headache might not seek healthcare or might take over-the-counter medications. Lastly, although the results of our study are consistent with reports on the possible role of childhood allergic diseases in the increase of migraine risk in children, there are still no biological plausibility and experimental explanation.

CONCLUSION

Our results support an association between early childhood allergic diseases and the occurrence of migraine on school age. The risk of migraine persistently increased with the number and severity of comorbid allergic diseases. Further research to understand the mechanism and pathogenesis between allergy and migraine is warranted.

Contributors C-CW and T-CS conceptualized and designed the study, drafted the initial manuscript, and approved the final manuscript as submitted. C-LL carried out the initial analysis, reviewed and revised the manuscript, and approved the final manuscript as submitted. C-CW and A-CC coordinated and supervised the data collection, critically reviewed the manuscript, and approved the final manuscript as submitted.

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Competing interests None declared.

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