# Association between Childhood Allergic Diseases and Headache

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J Pediatr Neurol 2020;00:1–6.

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## Abstract

Allergic disorders and headache are both common in pediatric populations. Chronic allergic disorders may affect sleep leading to chronic daily headaches. Poor controlled allergies may cause neurogenic inflammation that may be a predisposing factor to migraine headaches. We hypothesized that a higher prevalence of headaches may be found in children with allergy compared with those without allergy. Patients with either multiple allergic disorders or with poorly controlled allergic symptoms may be associated with headaches, especially migraine headaches. This study aimed to examine (1) the prevalence of headache in allergic children and (2) the association between allergic diseases and headache. Patients with allergic diseases and nonallergic children as control were recruited in the pediatric outpatient clinic of Naresuan University Hospital between January 2017 and January 2018. A neurological examination was performed by a pediatric neurologist. The questionnaire consisted of the pediatric headache symptom checklist and the items for evaluation of allergy control status. The diagnosis and classification of headache were based on the International Classification of Headache Disorders-3 criteria. The results were analyzed using the Student's t-test, chi-squared tests, odds ratios, and 95% confidence interval. One hundred fifty-five subjects were enrolled in our study, of which 85 subjects (54.8%) were diagnosed with allergic diseases. The allergic group had a significantly higher prevalence of headache than the control group (37 [43.5%] vs. 19 [27.1%], p ¼ 0.035). The allergic group also had a significantly higher prevalence of migraine and probable migraine headache than the control group (23 [27.06%] vs. 7 [10%], p ¼ 0.007). The prevalence of headache did not increase in subjects who had more than one allergic disease. There was no association between the control of allergy and headache. The present study showed that allergic diseases were associated with increased prevalence of headache and migraine in children. However, the control of allergic symptoms and the number of allergic diseases were not associated with headache. The physicians should be aware of headache in allergic patients and give appropriate treatment. Further study would be to identify specific biomarkers for the development of better treatment in these comorbid diseases.

Keywords
- headache
- migraine
- allergy
- allergic disorders

received
July 24, 2020
accepted
September 11, 2020



DOI https://doi.org/10.1055/s-0040-1718697.
ISSN 1304-2580.

## Background

The prevalence of allergic diseases including eczema, asthma, allergic rhinitis, allergic conjunctivitis, and atopic dermatitis is increasing worldwide. A recently published systematic review in children aged 0 to 18 years has shown the lifetime prevalence in the open population for eczema, asthma, and allergic rhinitis of 16.5 to 27.1%, 19.1 to 35.6%, and 18.3 to 47.7%, respectively.[1] Headache is also a common problem in children. The overall prevalence of headache in children and adolescents in the general population was 54.4% and the prevalence of migraine was 9.1%.[2] Both allergy and headache can affect psychological, physical, and social function which has an impact on the quality of life.[3–5]

Previous studies in adults have shown an increased prevalence rate of headaches especially migraine in patients with allergic rhinitis and asthma.[6–8] In pediatrics, few studies have been found. In childhood and adolescence, a high prevalence rate of headaches (odds ratio [OR] of 4.27) is associated with eczema with atopy.[7] Two pediatric studies have demonstrated that allergies are the risk factor for headache in school children (OR of 1.5),[9] and allergic rhinoconjunctivitis enhances migraine disability.[10] To date, the association of allergy and headache is not well understood. Genetic, environment, and systemic inflammatory response may contribute to headache in chronic allergic disease.[11] A population-based study evaluating the health-related quality of life (HRQoL) in adult headache patients has shown that this comorbid condition is associated with low HRQoL scores.[12]

This study aimed to investigate the prevalence of headache in allergic children. This work also studied the factors associated with headaches among children with allergic diseases, including allergic disease control, controlled medical treatment, and the number of affecting allergic diseases. We hypothesized that in children with allergic diseases, there might be a higher prevalence of headaches than in children without allergy. We also hypothesized that patients with either multiple allergic disorders or who had poorly controlled symptoms were associated with headaches, including migraine headaches.

## Methods

This study was approved by Naresuan University Institutional Review Board (NU-IRB 1034/59, COA.No.309/2017). Patients with allergic diseases such as allergic rhinitis, asthma, allergic conjunctivitis, and atopic dermatitis were recruited in the pediatric outpatient clinic of Naresuan University Hospital between January 2017 and January 2018. Nonallergic individuals were served as controls. The overall sample size (both cases and controls) was 110 based on a sample size calculation called two independent proportions (two-tailed test). All participants were informed and gave their consent before enrollment. All subjects and controls had undergone a complete neurological examination by a pediatric neurologist. The neurological examinations included a vital sign, consciousness, head circumference, eye examinations, a sign of meningitis, muscle tone and muscle power, deep tendon reflex and long tract sign, and cranial and carotid bruit. Examination of the ears, nose, and throat, as well as oral and dental health, was carried out to determine secondary causes of headache. Patients with abnormalities found by neurological examination were excluded from the study to avoid the interference of headache symptoms. Abnormal neurological findings or neurologic conditions that could contribute to headaches including head trauma, brain tumor, stroke, cerebral palsy, and seizure disorder were also excluded. The demographic data included age, gender, body weight, and height. The diagnosis of allergic diseases given by a pediatric allergist and the clinical symptoms of allergy was determined in terms of the onset of symptoms and medications used to control nasal, eye, and chest symptoms.

The questionnaire consisted of two parts. Part 1 was the pediatric headache symptom checklist and part 2 was for the evaluation of allergy control status. The questionnaire was validated by an index of item-objective congruence (IOC). The questionnaire was intended for children. However, in subjects younger than 7 years, the parents were the informer. The outcome measures in this present study were (1) the prevalence of headache in allergic children and (2) the association between allergic diseases and headache.

The headache diagnosis was determined by the pediatric headache symptom checklist, which had been validated by using the index of IOC. The pediatric headache symptom checklist consisted of a single question, for example, “Have you ever had a headache within 3 months?” To those who responded “yes,” the next remaining questions were involved in a more detailed assessment of headache characteristics. The 15-item questionnaires about headache consisted of frequency (once, more than one–four episodes, more than five episodes, every day), duration (1–15 minutes, 15–60 minutes, 1–4 hours, 4–24 hours, 24–48 hours, more than 48 hours), characteristic of headache (pulsatile or throbbing, tight band, others), headache location (unilateral temporal, bilateral temporal, frontal, around the eyes, diffuse, others), severity of headache: limitation in daily activities (yes, no), progression of headache symptoms (yes, no), timing of headache (day, night), associated symptoms (fever, nausea, vomiting, photophobia, phonophobia, numbness, weakness, other), precipitating and aggravating headache factors (stress, exercise, sleep deprivation, menstruation, others), factors that make headaches worsen (bright light, sounds, straining during defecation or coughing, change of position, others), factors that make headaches improved (rest or sleep, analgesics, others), aura: visual signs and symptoms (blind spots, changes in vision or visual loss, flashes of light), sensory disturbances (numbness), prior therapy (medications and nonmedication), history of head injury (yes, no), and medical history and family history (migraine, chronic headache, brain tumor, other). The diagnosis and classification of primary headache are based on the International Classification of Headache Disorders (ICHD)-3 criteria.

Asthma control was assessed according to the 2018 Global Initiative for Asthma. Well-controlled allergic rhinitis was defined as no allergic nasal symptoms without nasal decongestant usage, normal sleep, or no impairment of daily activities within 1 month. Well-controlled allergic conjunctivitis was defined as no allergic ocular symptoms including redness, edema or swelling of the conjunctiva, itching, and increased lacrimation within 1 month. The comorbid conditions such as acute or chronic sinusitis, autistic, attention-deficit hyperactivity disorder (ADHD), adenotonsillar hypertrophy, snoring, and obstructive sleep apnea were studied from medical records and patient declarations.

Data were analyzed using SPSS version 17.0. The Student's t-test was used to compare the mean age and body mass index (BMI) between the two groups. The chi-squared tests, ORs, and 95% confidence interval (CI) were used to analyze the association of headache between the allergy group and the control group. The p-values of less than 0.05 were regarded as statistically significant.

## Results

One hundred fifty-five subjects were enrolled in this study. There were 85 allergic subjects and 70 control subjects. Males in the allergic group and control group were 63.5% (54/85) and 48.6% (34/70).

The average age of the allergic group and nonallergic group was 117.9 and 114.5 months. There were no significant differences in sex, age, and BMI between allergic subjects and controls. None of the patients and controls had abnormal vital signs or neurological examination. There were only four patients (2.6%) whose parents reported symptoms of snoring. Other comorbidities such as acute or chronic sinusitis, noncyanotic heart disease, thalassemia, glucose-6-phosphate dehydrogenase deficiency, and ADHD were reported, as shown in ►Table 1.

Among allergic subjects, there were 76.5% of allergic rhinitis, 50.6% of asthma, 15.3% of allergic dermatitis, and 10.6% of allergic conjunctivitis. Thirty-five (41.2%) of 85 subjects had more than one allergic diseases as shown in ►Table 2. Thirty-seven (43.6%) of 85 subjects were well controlled. Inhaled corticosteroid therapy or intranasal corticosteroid (89.4%) and oral H1 antihistamine (54.2%) were used as long-term controller medications.

The allergic group had a significantly higher prevalence of headache than the control group (37 [43.5%] vs. 19 [27.1%], p ¼ 0.035), with OR of 2.1 (95% CI: 1.049–4.081). Only 5 of 85 allergic subjects were diagnosed with migraines. However, 18 of 85 subjected had incomplete ICHD-3 criteria for migraine diagnosis, and therefore, they were diagnosed as probable migraine. Among these 18 patients, 3 patients had less than five attacks, 3 patients had the duration of headache less than 1 hour, 3 patients had a nontemporal location of headache, 9 patients had no nausea, vomiting, photophobia, or phonophobia.

Overall, the allergic group had a significantly higher prevalence of migraine and probable migraine headache than the control group (23 [27.06%] vs. 7 [10%], p ¼ 0.007), with OR of 3.3 (95% CI: 1.366–8.343). The allergic group had a higher prevalence of tension and probable tension-type headache %) than the control group (1.43%), but the difference was not statistically significant (p ¼ 0.057) (►Table 3).

However, neither the types of allergic diseases nor having more than one allergic disease increased the prevalence of headache, as shown in ►Table 2. For the control of allergic symptoms, the symptom control and the usage of antihistamine or inhaled corticosteroids were not correlated with headache (p ¼ 0.299 and p ¼ 0.953, respectively).

Table 1 Demographic characteristics of study population

| Demographic data | Allergy group (n ¼ 85) | Nonallergy group (n ¼ 70) | p-Value |
|---|---|---|---|
| Gender | | | |
| Male | 54 (63.5%) | 34 (48.6%) | 0.06 |
| Female | 31 (36.5%) | 36 (51.4%) | |
| Mean age ± 2 SD (mo) | 115.2 ± 25.3 | 114.5 ± 30.4 | 0.35 |
| Mean BMI ± 2 SD (kg/m$^2$) | 19.0±4.8 | 17.9±5.5 | 0.49 |
| Comorbid diseases | | | |
| G-6-PD deficiency | 1 (1.2%) | 2 (2.9%) | |
| Thalassemia minor | 1 (1.2%) | 1 (1.4%) | |
| ADHD | 5 (5.9%) | 3 (4.3%) | |
| Snoring | 1 (1.2%) | 3 (4.3%) | |
| Congenital heart disease | 1 (1.2%) | 0 | |

Abbreviations: ADHD, attention-deficit hyperactivity disorder; BMI, body mass index; G-6-PD, glucose-6-phosphate dehydrogenase; SD, standard deviation.

## Discussion

The results of our study are in agreement with those of previous studies in adults and children[6–12] in that the prevalence of headache was higher in the allergic group than the nonallergic group. Our allergic group consisted of various types of allergy including allergic rhinitis, asthma, atopic dermatitis, and atopic conjunctivitis. Up to 34 subjects had more than one allergic disease, which is commonly found in allergic patients. For the types of headache, migraine headache was found to increase significantly in the allergic group. However, tension headache insignificantly increased, which was likely due to a small number of patients having tension headaches.

We found that poorly controlled allergic diseases were not associated with any type of headache.

This differed from the study in adult asthma.[6] The explanation might be that our study had various types of allergic diseases not only asthma. Also, this study showed that migraine headache was not significantly correlated with the use of inhaled corticosteroids. This finding was similar to previous adult asthma study,[13] although our study included both nasal and inhaled corticosteroids for the treatment of allergic rhinitis and asthma. A previous report has suggested that the types and dosage used of inhaled corticosteroids could systemically affect the central nervous system in different ways leading to migraine headache.[14]

The mechanism of allergy-causing headaches is not known. Allergic rhinitis symptoms such as sneezing,

Table 2 Associated factors of headache in allergic children

| Associated factors of headache | Headache, n (%) | No headache, n (%) | OR | 95% CI | p-Value |
|---|---|---|---|---|---|
| Types of allergic diseases | | | | | |
| Allergic rhinitis | 34 (40%) | 31 (36.5%) | 1.3 | 0.490–3.667 | 0.568 |
| Asthma | 22 (25.9%) | 21 (24.7%) | 1.0 | 0.448–2.452 | 0.915 |
| Allergic dermatitis | 6 (7.1%) | 6 (7.1%) | 1.4 | 0.399–4.603 | 0.062 |
| Allergic conjunctivitis | 6 (7.1%) | 2 (2.4%) | 4.5 | 0.843–23.503 | 0.059 |
| Number of allergic diseases per person | | | | | |
| One type of allergy | 18 (21.2%) | 33 (38.8%) | 0.4 | 0.177–1.046 | 0.061 |
| More than one type of allergic disease | 19 (22.4%) | 15 (17.6%) | | | |
| The control of allergies | | | | | |
| Well controlled | 14 (16.5%) | 23 (27.1%) | 0.7 | 0.276–1.584 | 0.353 |
| Not controlled | 23 (27.1%) | 25 (29.4%) | | | |
| Long-term control medications | | | | | |
| Oral H1 antihistamines | 23 (27.1%) | 23 (56.5%) | 0.6 | 0.234–1.341 | 0.299 |
| Inhaled corticosteroid | 33 (38.8%) | 43 (50.6%) | 1.0 | 0.259–4.189 | 0.953 |

Abbreviations: CI, confidence interval; OR, odds ratio.
Note: p-Value considered significant at :::0.05.

pruritus, rhinorrhea, and nasal congestion frequently disrupt nocturnal sleep. The fatigue and sleep disturbances that occur in patients with allergic disorders could increase the risk of headache.[7] The correlation between sleep disorders and chronic headache is bidirectional. Impaired sleep might lead to tension-type headaches and can also exacerbate migraine attacks. On the contrary, migraine and tension-type headaches may cause sleep disturbance in children.[15,16] In our study, only four children had snoring and other causes of sleep disturbance were not found. The sleep assessment by self-report might not be reliable and, hence, the sleep apnea screening questionnaires or sleep test would be applied in the next study. The use of daily diaries may be beneficial for a better record in headache characteristics.

The relationships between migraine headaches and allergy have been explored widely. Genetics and several triggers such as diet, smoking, stress, exercise, environmental factors, and pollution have been shown to share common pathophysiological mechanisms in both migraine-type headache and atopic disorders.[11] Many studies have informed that immune dysfunction and neurogenic inflammation might play potential roles in the relationship between these two comorbid diseases.

Allergens, immunoglobulin E–mediated mechanism, and histamine could also play roles in migraine.[17–19] The positive allergy tests in the migraine group are significantly higher than the healthy group.[15] Among patients with migraine, the frequency of migraine attacks is higher in patients with positive allergy tests for house dust, red birch, hazel tree, olive tree, nettle, and wheat than those with negative allergy tests. The mast cells in the dura mater activated by the allergens release the inflammatory mediators, which affect the vasodilator phase of the migraine attack.[17] Migraine patients with more allergen sensitization may have more migraine attacks.[17] Nevertheless, the present study did not assess the correlation between allergy and the frequency of migraine attacks.

Migraine is a complex neurovascular disorder. Many studies have focused on the pain sensitization aggravated by the immune response.[20–22] Migraine might be involved in

Table 3 Prevalence of headache, types of headache, and the association between headache and allergy

| Headache | Allergy group (n ¼ 85) | Nonallergy group (n ¼ 70) | OR | 95% CI | p-Value |
|---|---|---|---|---|---|
| Headache | 37 (43.52%) | 19 (27.14%) | 2.1 | 1.049–4.081 | 0.035 |
| Types of headache | | | | | |
| Migraines and probable migraine | 23 (27.06%) | 7 (10%) | 3.3 | 1.336–8.343 | 0.007 |
| Tension-type headache | 7 (8.24%) | 1 (1.43%) | 6.2 | 0.743–1.598 | 0.057 |
| Headache due to acute illness | 3 (3.53%) | 1 (1.43%) | 2.5 | 0.257–4.821 | 0.412 |
| Nonspecific headache | 4 (4.71%) | 8 (11.43%) | 0.4 | 0.110–1.329 | 0.119 |

Abbreviations: CI, confidence interval; OR, odds ratio.
Note: p-Value considered significant at :::0.05.

either systemic inflammation or immune response in allergic children. Neuropeptides, such as calcitonin gene-related peptide (CGRP), substance P (SP), pituitary adenylate cyclase-activating polypeptide, somatostatin, and neuropeptide Y, are released by large secretory vesicles from terminal activated nociceptive trigeminal (trigeminal nucleus caudalis[Q8] [TNC]) nerve, subsequently initiate sterile neurogenic inflammation. The neurogenic inflammation is associated with the interaction between these peptides and blood vessels, neurons, and immunocytes leading to vasodilatation, plasma extravasation, trigeminal satellite glial cell activation, and mast cell degranulation. The sensory and autonomic neurons can be sensitized and induce the migraine attack.

Histamine, a proinflammatory mediator released by mast cells upon degranulation, activates the acid-sensing ion channels that prolong trigeminally and TNC neuron activation.[20] Intravenous histamine could induce headaches and aggravate migraine headache.[21,22] In this study, long-term treatment with first-generation H1 antihistamines and second-generation H1 antihistamines in allergic patients was not associated with migraine. This might be explained that both H1 antagonist and H2 antagonist have poor blood–brain barrier (BBB) permeability.[23] Activation of specific target H3R by Nα-methylhistamine, a potent H3R agonist, could inhibit CGRP and SP release, modulating the release of neurotransmitter and neuropeptide. Nα-methylhistamine can pass through the BBB, thus it may be effective in allergic patients with migraine management.[22,24]

## Conclusion

The present study showed that allergic diseases were associated with increased headache and migraine in children. However, the control of allergic symptoms and the number of allergic diseases were not associated with headache. Physicians should be aware of headache symptoms in allergic patients and give appropriate treatment. Further study would be to identify specific biomarkers for the development of better treatment in these comorbid diseases.

### Funding

This work was financially supported by a research grant from the Faculty of Medicine, Naresuan University, Grant No. R2562C006.

### Conflict of Interest

None declared.

### Acknowledgments

The authors would like to thank Assoc. Prof. Dr. Sutatip Pongcharoen, Department of Medicine, Faculty of Medicine, Naresuan University, Phitsanulok, Thailand, for restructuring and modifying the contents of the manuscript as well as the English grammar editing. Also, special thanks to Miss Kornthip Jeephet, Statistics Technical Officer, Research Center, Faculty of Medicine, Naresuan University, for her valuable assistance with the statistics used in this report.

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