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Original Article

Association between allergic diseases, allergic sensitization and attention-deficit/hyperactivity disorder in children: A large-scale, population-based study

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Abstract

Background: Increasing prevalence of allergic diseases has been matched by parallel trends in attention-deficit/hyperactivity disorder (ADHD). However, previous studies concerning the association between ADHD and allergic diseases have been inconsistent. Moreover, it is not clear whether this association is modified by allergic sensitization status. Therefore, we evaluated the association between allergic diseases, allergic sensitization, and ADHD in children.

Methods: We conducted a large-scale cross-sectional, population-based survey to investigate the relationship between allergic diseases, allergic sensitization, and ADHD. Children aged between 3 and 6 years were selected from kindergartens, and received skin prick tests (SPTs) for mite, cockroach, dog, milk, egg, and crab allergens. Information about allergic diseases, environmental exposures, and physician-diagnosed ADHD were collected. Multiple logistic regressions were performed to estimate the association between allergic diseases and ADHD, with adjustments made for potential confounders.

Result: A total of 2772 children were found to be eligible for analysis; of these 411 (14.8%) had atopic dermatitis (AD), 954 (34.4%) had allergic rhinitis (AR), 451 (16.3%) had asthma, and 28 (1.01%) had ADHD. Children who had AD and asthma with allergic sensitization were found to be at increased risk for ADHD, with adjusted ORs (95% CI) of 4.50 (1.28–15.86) and 3.65 (1.07–12.49). Children who had AR, allergic conjunctivitis, or food allergies were also related to ADHD, though failed to reach statistical significance.

Conclusion: Our results suggest that AD and asthma with allergic sensitization are associated with ADHD in children. As allergic sensitization is an increased factor of developing allergic diseases, early control of environmental and allergens exposure could help to modify the burden of ADHD.

Keywords: ADHD; Asthma; Atopic disorders

1. Introduction

Attention-deficit/hyperactivity disorder (ADHD) is the most common behavioral disorder in children.[1] The prevalence of ADHD is increasing in many countries, including Taiwan.[2] The cumulative prevalence of ADHD diagnosis

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increased from 0.06 to 1.64% from 1996 to 2005 in Taiwan, but the reasons for the rise are still undetermined.[2] Prevalence of ADHD was reported from 1.0% to 7% in school-aged children all over the world, and was three times more likely to occur in boys compared to girls.[2,3] Recognizable symptoms of ADHD include difficulties with attention, impulsivity, and hyperactivity.[4,5] ADHD is a genetically complex and highly heritable brain disorder; however, it is still unclear how specific genes interact with adverse environmental factors and lead to the various brain abnormalities observed in ADHD.[3,6,7]

In 2004, the Global Initiative of Asthma estimated that more than 300 million people worldwide and 7−15% of children are affected by asthma, making it the leading cause of childhood chronic medical illness.[8] However, the prevalence of other allergic diseases, including atopic dermatitis (AD) and allergic rhinitis (AR), is also increasing,[8] with the global prevalence of childhood AR reported to be as high as 39.7%.[5,7,8] Children with allergic diseases have greater difficulty in school.[9,10] Their often-described hyperactive and impulsive behaviors have been thought to be secondary to these chronic illnesses or their treatment.[11] However, research regarding the association between ADHD and allergic diseases is often conflicting.[5,12−15]

Allergic sensitization is an important risk factor for the development and severity of allergic diseases.[3−6] The association between ADHD and allergic sensitization was sourced in comorbidity or causality has been discussed in some studies,[2−6] but the exact relationship between allergens exposure and ADHD is unclear. Both ADHD and allergic sensitization depend on a complex interaction between genetic and environmental factors. If allergic sensitization is associated with ADHD, prevention of allergic sensitization might play a role in decreasing the burden of ADHD.[2−6] Although some studies have presented the association between ADHD and allergic diseases or allergic sensitization, the data of the most published studies were small-scale, meta-analysis or analyzing health insurance database.[3−6] This is the first large-scale, population-based study for better understanding the association between ADHD, allergic diseases and allergic sensitization. We conducted a cross-sectional survey on 2772 children to investigate the relationship between allergic diseases, allergic sensitization (positive SPTs), and ADHD.

2. Methods

2.1. Study population

We conducted a population-based, cross-sectional survey on kindergarten children (aged 3−6 years) residing in 11 communities in Taiwan in 2010.[16] A total of 3264 school children (i.e. the Childhood Environment and Allergic diseases Study CEAS cohort) were recruited. After excluding subjects without skin prick test (SPT) results (N = 435), with multiple gestations (N = 27), and inability to answer questions in Chinese (N = 30), 2772 participants were found to be eligible for this study. The informed consents of providing the questionnaire and SPT were obtained from the parents or guardians. The study protocol was approved by the Institutional Review Board of Taipei Hospital (IRB No.: TH-IRB-09-04) and complied with the principles outlined in the Helsinki Declaration.

2.2. Case definitions

Parents or guardians were asked to complete the standardized questionnaire. Cases of AD were defined by positive responses to the questions: “Has your child ever had AD diagnosed by a physician?” and “Has your child ever had recurrent itchy rash for at least 6 consecutive half-month periods over elbows, knees, face, wrists, neck, periauricular and eyebrow areas?” Cases of asthma were defined as a positive response to “physician-diagnosed asthma”, together with a positive response to nocturnal cough or exercise-induced wheeze over the past 12 months. Cases of AR were defined by positive responses to the questions “Has your child ever been diagnosed as having AR by a physician?” and “Has your child ever had a problem with sneezing, or a runny or blocked nose, when your child did not have a cold or the flu?”

Cases of allergic conjunctivitis were defined by positive responses to the questions “Has your child ever been diagnosed as having allergic conjunctivitis by a physician?” and “Has your child ever had a problem with recurrent itching, redness, burning or tearing of the conjunctivas?” Cases of food allergy were defined by positive responses to the questions “Has your child ever been diagnosed as having food allergy by a physician?” and “Has your child ever had a problem with itching in the mouth, eczema, swelling of the lips, face, tongue and throat or other parts of the body, wheezing, nasal congestion, or trouble breathing due to particular foods?” Children with ADHD show a persistent pattern of inattention and hyperactivity-impulsivity behaviors were defined according to the criteria of the American Psychiatric Association's Diagnostic and Statistical Manual, Forth edition (DSM-4).[1,2,4,5] The conditions of disease in children were confirmed by board-certified child psychiatrists or pediatric neurologists, according to the clinical evaluation.[1,2,4,5]

2.3. Exposure measurements

The standard ISAAC-Chinese version questionnaire with additional questions concerning environmental allergen exposures was answered by the parents. The questionnaire also contained questions on basic demography, residential environmental factors (such as environmental tobacco smoking, pets and cockroaches at home, dampness of the house, fungus on the house wall, and carpets at home), and family history of atopic diseases.

2.4. Laboratory methods

Allergic sensitizations were defined by SPTs on 6 common allergens, including house dust mites (HDMs mix, including Der p, Der f, Der m, and Blot allergens), cockroaches, dog dander, milk, egg, and crab allergens (ALK-Abello, Round

Rock, TX, USA). A positive SPT result indicates positive reaction to at least one of the six allergens, identified by development of itchiness at the site of injection followed by redness and swelling with a wheal at the center. Histamine (0.1%) in phosphate buffered saline and normal saline were used as positive and negative controls, respectively. Children were advised not to take antihistamines for 72 h before their clinic appointments. The tests were read at 15 min, and mean wheal diameters were calculated (sum of the longest diameter and the diameter perpendicular to it divided by 2). For positive control patients, a mean wheal diameter exceeding the negative control wheal diameter by at least 3 mm was deemed to be a positive result.

2.5. Statistical analysis

Multiple logistic regression analysis was performed to assess the association between allergen sensitizations, allergic diseases, and the risk of ADHD, with adjustments made for potential confounders. Odds ratios (ORs) with 95% confidence intervals (95% CIs) were calculated by logistic regression. Potential confounders from literature reviews (such as gender, premature birth, maternal age and education, maternal history of atopy, family income, duration of breast feeding, number of older siblings, pet raising, ETS exposure, usage of carpets at home, and fungi on house walls) were taken into consideration. Adjustments made for these confounders resulted in a 10% change of point estimates in the model. All hypothesis testing was two-sided at a significance level of 0.05 and was performed with SAS software version 9.1 (SAS Institute, Cary, NC, USA).

3. Results

A total of 2772 children were enrolled in this study. The baseline characteristics for participants (with SPTs, N = 2772) and comparisons will all eligible participants (N = 3246) are as presented in Table 1. The relationship between characteristics, environmental factors and ADHD is shown in Table 2. Of our subjects, 28 were diagnosed with ADHD (1.01%). The risk of ADHD was found to be higher for boys (crude OR 2.79, 95% CI 1.11−7.01) and for those who had been sent to day-care centers when they were less than a year old (OR 2.53, 95% CI 1.14−5.56). There were no other significant differences between ADHD and non-ADHD children (Table 2).

Our results show that 179 (6.5%) of our 411 (14.8%) AD patients were SPT-positive, 197 (7.1%) of our 451 (16.3%) asthma patients were SPT-positive, 395 (14.2%) of our 954 (34.4%) AR patients were SPT-positive, 190 (6.9%) of our 328 (11.8%) allergic conjunctivitis patients were SPT-positive, and 175 (6.6%) of our 314 (11.9%) food allergy patients were SPT-positive. SPT-positive patients, along with the 28 (1.01%) ADHD patients, were deemed to be eligible for inclusion in the analysis (Table 3). AD with allergic sensitization (adjusted OR 4.50, 95% CI 1.28−15.86) and asthma with allergic sensitization (adjusted OR 3.65, 95% CI 1.07−12.49) were found to be significantly associated with ADHD. AR, allergic conjunctivitis, and food allergy with allergic sensitization were associated with ADHD, but the association failed to reach statistical significance (Table 3). ADHD was not found to be significantly associated with AD, AR, or asthma without allergic sensitization (Table 3). Among all SPTs, only mite

Table 1
Baseline characteristics of the participants (N = 2772), comparing with dropout (N = 3246) analysis.

	N = 2772		All eligible participants (N = 3246)		*p*
	N	%	N	%	
Characteristics of the mother					
Maternal age at the birth of the child ≥34 years (%)	414	15.8	503	16.6	0.463
Maternal education ≥ College (%)	757	28.2	858	27.7	0.469
Maternal history of atopy (yes, %)	1044	41.4	1205	41.4	0.666
Characteristics of the children					
Male gender (%)	1478	53.4	1747	54.1	0.639
Birth weight <2500 gm (%)	165	6.3	196	6.6	0.721
Gestational age <37 weeks (%)	235	8.6	264	8.4	0.809
Parity <2 (%)	2211	72.3	2527	81.5	0.467
Environmental factors					
Breast feeding (yes, %)	2071	75.2	2311	74.7	0.676
Incensing at home (yes, %)	1434	53.9	1633	53.8	0.977
Environmental tobacco smoke exposure (yes, %)	1529	57.4	1781	57.8	0.628
Family income per year[a]					
< 600,000 NT dollars (%)	886	32.0	1059	32.6	0.336
600,000−1,500,000 NT dollars (%)	1366	49.3	1542	47.5	
> 1,500,000 NT dollars (%)	218	7.9	249	7.7	
Allergic diseases					
Allergic dermatitis (yes, %)	411	14.8	568	17.6	0.293
Asthma (yes, %)	451	16.3	1157	35.8	0.353
Allergic rhinitis (yes, %)	954	34.4	495	15.3	0.773
Allergic conjunctivitis (yes, %)	328	11.8	382	19.5	0.931
Food allergy (yes, %)	314	11.3	375	11.6	0.948

[a] New Taiwan (NT) dollars per year ($1 USD = $ 31 New Taiwan dollar).

Table 2
The association between characteristics of the participants and ADHD.

	N	%	ADHD
			Crude OR (95% CI)[a]
Characteristics of the mother			
Maternal age at the birth of the child ≥34 years (%)	414	15.8	1.02 (0.35–2.98)
Maternal education ≥ College (%)	757	28.2	0.48 (0.17–1.41)
Maternal nationality (Taiwanese,%)	2521	93.4	0.82 (0.19–3.48)
Maternal history of atopic disorders (yes, %)	1044	41.4	1.01 (0.45–2.29)
Characteristics of the children			
Male gender (%)	1478	53.4	2.79 (1.11–7.01)
Birth weight <2500 gm (%)	165	6.3	1.48 (0.34–6.40)
Gestational age <37 weeks (%)	235	8.5	1.54 (0.43–4.88)
Parity <2 (%)	2211	79.8	1.13 (0.39–3.30)
Environmental factors			
Breast feeding (yes, %)	2071	75.2	0.85 (0.35–2.04)
Incensing at home (yes, %)	1434	53.9	0.79 (0.36–1.74)
Environmental tobacco smoke exposure (yes, %)	1529	57.4	2.37 (0.94–5.95)
Day care <1 years old (yes, %)	636	23.9	2.53 (1.14–5.56)
Furry pets at home (yes, %)	467	17.5	0.20 (0.26–1.45)
Family income per year[b]			
< 600,000 NT dollars (%)	886	32.0	1
600,000–1,500,000 NT dollars (%)	1366	49.3	0.54 (0.23–1.25)
> 1,500,000 NT dollars (%)	218	7.9	–

[a] OR = odds ratio; CI = confidence interval.
[b] New Taiwan (NT) dollars per year ($1 USD = $ 31 New Taiwan dollar).

Table 3
The relationship between allergic diseases, allergic sensitization and ADHD.

Atopic disorders	N^	%	ADHD	
			Crude OR[a] (95% CI)	Adjusted OR[b] (95% CI)
Atopic dermatitis				
(−)	2361	85.2	–	–
(+) non-sensitization	232	8.4	2.74 (0.90–8.34)	1.71 (0.44–6.60)
sensitization	179	6.5	5.42 (2.08–14.16)[a]	4.50 (1.28–15.86)[a]
Asthma[c]				
(−)	2320	83.7	–	–
(+) non-sensitization	255	9.2	3.07 (1.11–8.53)[a]	2.35 (0.65–8.49)
sensitization	197	7.1	4.00 (1.44–11.13)[a]	3.65 (1.07–12.49)[a]
Allergic rhinitis[c]				
(−)	1818	65.6	–	–
(+) non-sensitization	559	20.2	2.29 (0.87–6.05)	1.43 (0.44–4.67)
sensitization	395	14.2	3.74 (1.47–9.53)[a]	1.91 (0.55–6.62)
Allergic conjunctivitis				
(−)	2444	88.2	1	1
(+) non-sensitization	138	5	1.45 (0.33–6.44)	1.54 (0.35–6.86)
sensitization	190	6.8	1.05 (0.24–4.65)	1.05 (0.24–4.65)
Food allergy				
(−)	2458	88.7	1	1
(+) non-sensitization	139	5	1.78(0.41–7.70)	1.94(0.44–8.46)
sensitization	175	6.3	2.12(0.62–7.24)	2.01(0.59–6.90)

N^, number of screened children.
[a] OR = odds ratio; CI = confidence interval.
[b] Adjusted for age, gender, maternal history of atopic disorders, birth weight, maternal education and duration of breast feeding.
[c] Adjusted for the above-mentioned variables and the diagnosis of AD at the age of 3 years.

sensitization was found to be significantly associated with ADHD (adjusted OR 2.90, 95% CI 1.10–7.69) (Table 4).

4. Discussion

This study is the first large-scale study demonstrating a strong positive association between ADHD and allergic sensitization as diagnosed by positive SPTs. After stratification by allergic sensitization, ADHD was found to be associated with allergic diseases with sensitization. Our study found that AD with allergic sensitization and asthma with allergic sensitization were both significantly associated with ADHD; this was particularly true for mite sensitization. Our results contribute to better understanding of the etiology of ADHD and may initiate new points of view for early prevention.

AD, asthma, and ADHD are common pediatric diseases associated with learning difficulties and sleep disturbances.[17,18] Prior studies have shown that AD and ADHD are positively associated.[5,19] However, despite considerable research, the etiology and pathophysiology of ADHD remain unclear.[12,20] In the absence of major genetic effects, the etiology is believed to involve multiple genes whose expression is modified by environmental factors.[20,21] Neurochemical investigations also point to a catecholaminergic disturbance in ADHD,[22] yet the mechanisms underlying such a metabolic abnormality are still unknown.[20,21]

We found AD with allergic sensitization to be associated with ADHD. Some pathways can account for the increased risk of ADHD among children with AD.[23] It is widely accepted that the hallmark pathology of AD is immunologic irregularities such as high immunoglobulin-E (IgE), increased eosinophilic activity and a predominantly T helper type 2 (TH2) cytokine secretion.[25] Consequently, children with AD start to be exposed to increased levels of proinflammatory cytokines, including interleukin (IL)-1, IL-6, tumor necrosis factor-*a* during early infancy.[3–6,25,26] A growing number of studies further suggest that inflammatory cytokines released during the atopic response may pass the blood–brain barrier and activate neuroimmune mechanisms (such as stress)that have behavioral and emotional relevance.[24] AD is thus associated with high levels of psychological stress that may lead to dysfunctional mother–child relationships, sleep disturbances, less physical contact, and later stigmatization and bullying by peer groups.[28] Such an increased level of everyday stress starts early in infancy with the onset of AD; prior studies in humans have clearly indicated that the brain is particularly sensitive to stress during the early years as it is undergoing dramatic change during that period.[26,28] Furthermore, sleep disturbances are common in infants or children with AD.[26,28] Because sleep is vital for brain development and is linked to higher mental development scores,[29,39] our study findings indicate that increased stress exposure from adverse parenting or disturbed sleep patterns during early infancy can affect multiple neurotransmitter and neuroendocrine systems, which then lead to long-term alterations in the behavioral and physiological repertoire, thereby increasing vulnerability to psychopathological conditions such as ADHD.[30,39]

Table 4
The association between allergens sensitization and ADHD.

	Skin prick test	Inhaled allergen						Food allergen					
		Mite		Cockroach		Dog dander		Milk		Egg		Crab	
		(−)	(+)	(−)	(+)	(−)	(+)	(−)	(+)	(−)	(+)	(−)	(+)
ADHD	Crude OR	1	2.41	1	0.93	1	1.25	1	1.60	1	1.89	1	1.12
	(95% CI)		(1.02−5.70)[a]		(0.28−3.15)		(0.29−5.37)		(0.59−4.33)		(0.70−5.12)		(0.33−3.77)
	Adjusted OR[a]	1	2.90	1	1.29	1	1.60	1	1.06	1	1.22	1	0.90
	(95% CI)		(1.10−7.69)[a]		(0.37−4.46)		(0.36−7.04)		(0.31−3.68)		(0.35−4.24)		(0.21−3.93)

[a] Adjusted for age, gender, maternal history of atopic diseases, birth weight, maternal education and duration of breast feeding.

Our study also showed asthma with allergic sensitization to be a risk factor for ADHD. The mechanism underlying the development of ADHD in children with asthma is unclear; however, Christakou et al. showed that boys with ADHD had significantly reduced activation of the bilateral striato-thalamic regions and the left dorsolateral prefrontal cortex during a vigilance task.[31] Liu et al. revealed that male ADHD patients exhibited hyperactivity of the anterior cingulate gyrus during the Go/no-Go task, which correlates with the ratings for impulsivity.[32] Some studies also found that children with asthma and ADHD had similar brain region dysfunctions.[22,27,31−34] Parker et al. further reported that patients with asthma had a higher rate of white matter hyper density and abnormal anatomic findings. The above-mentioned findings indicate that elevated brain activity can be attributed to inflammation, which plays a key role in both ADHD and allergic asthma.[22]

Our study showed that AD and asthma with allergic sensitization were significantly associated with ADHD, but AD and asthma without allergic sensitization were not. Many studies have found the severity of AD and asthma to be influenced by allergic sensitization. Severe AD and asthma patients react more strongly or to a larger panel of allergens than patients with milder diseases. Some studies suggest that patients with severe AD and asthma have broader IgE recognition profiles or higher IgE levels, which might indicate that severe AD and asthma patients are more atopic compared to those with milder diseases.[35−39] It could be that patients with AD and asthma with allergic sensitization are more sensitive to disturbing factors due to higher levels of cytokines, IgE, or higher levels of psychological stress, and so have a higher significant association with ADHD.[39]

Food allergies are becoming increasingly prevalent worldwide, with prevalence estimates ranging from 2% to 8%. A recent National Health and Nutrition Examination Survey (NHANES) that employed specific serum IgE levels as an indicator estimated the prevalence of clinical food allergies to four common allergens (peanut, milk, egg, shrimp) at about 2.5% for the US general population, with higher rates in 1−5 year-old (4.2%). Some studies have shown that children with food allergies exhibited at least one symptom of emotional, disruptive, and eating disorder psychopathologies; these children also had higher frequencies of depression and generalized anxiety that increased over time. This phenomenon might be related to disturbances in catecholaminergic regulatory mechanisms, as evidenced by high cortisol, epinephrine, and norepinephrine, and IgE-mediated inflammatory response. However, we did not find a positive relationship between food allergens and ADHD in this study, and no prior large-scale studies have demonstrated the above-mentioned relationship among children with ADHD. Possible explanations for such a discrepancy may be that the number of subjects testing positive to food allergies in our study was relative small and also that food sensitivity should be observed over a longer period of time. Longer follow-up schedules may be needed to elucidate the association with food allergies and ADHD.[34]

Interestingly, our study showed that mite sensitization was significantly associated with ADHD. House dust mites are the most important airborne allergen and can be a major perennial allergen source and a significant cause of AR and AD. Early oral exposure to house dust mite allergens through breast milk can also be an important potential risk factor for allergic sensitization and respiratory allergies in children. Infant exposure to mites (the most common indoor allergen) is probably more common compared to cockroach, dog dander, milk, egg, and crab allergens.[20,38,39]

Many studies have tried to examine the associating factors of atopic severity and disease persistence. Early-onset allergic diseases for patients less than a year old were found to be an unfavorable factors,[4,6,13,20,38,39] indicating that if children are persistently exposed to mites early in life, this could have more disturbing consequences. Some studies also found that stress-related inflammatory cytokines may pass the blood−-brain barrier and activate neuroimmune mechanisms that have behavioral and emotional relevance.[13,24−26,40,41] For young infants, that might be more threatening than older children. Those could be why mite sensitization was the only allergen associated with ADHD in our study. Further evaluation and longer follow-up study were needed for the conclusion.

Accumulated data indicates that ADHD might be a comorbidity of allergic diseases.[4,6,12,14,24,39] The increasing prevalence of allergic diseases and ADHD, as well as the enormous costs of both diseases in terms of human suffering and their economic impacts make it imperative to acknowledge the reality of this comorbidity in order to modify its course.[2,12,14,24,39] As allergic sensitization is essential in the development of allergic diseases, allergic sensitization is also assumed to play a critical role in ADHD.

There are some limitations of this study. The prevalence of ADHD in this study was lower than the prevalence in other countries.[1,2] Underestimation of the prevalence due to recall bias of "parent-reported doctor-diagnosed ADHD" in this population-based study may account for this finding.[2,12,21] Additionally, different ethnicities, age groups, study populations, and study designs across different countries could provide alternative explanations for the observed discrepancy.[1,2] However, the underestimation in prevalence is likely to be a non-differential misclassification which biased estimates toward the null. Finally, this is a cross-sectional survey so causal relationships could not be established. Further follow-up of this cohort is warranted to elucidate causal associations.

This study is the first and largest population-based survey demonstrating the relationship between allergic diseases, allergen sensitization confirmed by SPTs, and ADHD. We demonstrated that AD and asthma with allergic sensitization were associated with ADHD. Control of allergens exposure might be a critical factor influencing the development of ADHD.

In Conclusions our results found that allergic diseases with sensitization were significantly associated with ADHD. Further studies are required to elucidate the pathophysiology underlying the relationship between allergic diseases, allergic sensitization, and ADHD. The increasing prevalence of ADHD carries a great health burden to children. Since allergic sensitization is essential in the development of allergic diseases, early control of environmental and allergen exposure might modify the subsequent burden of ADHD.

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