Association between Allergic Sensitization and Attention Deficit Hyperactivity Disorder (ADHD)

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Summary

Background: **The increase in prevalence and burden of allergic diseases, i.e., eczema, asthma, and rhinitis, has been matched by parallel trends in a worldwide increase in attention deficit hyperactivity disorder (ADHD) diagnoses. Research data concerning the causal association between ADHD and allergies are conflicting. Allergic sensitization is the most important risk for development of allergic diseases.**

Objective: **We investigated the relationship between allergic sensitization in patients with physician-diagnosed ADHD.**

Methods: **Eighty patients were enrolled in the study. Forty patients were allocated into the ADHD group who presented with a Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition diagnosis of ADHD to an outpatient pediatric developmental and behavioral clinic and the other 40 were enrolled in the control group. All patients were performed skin prick testing to common allergens and were evaluated for allergic diseases with focused history and physical examination.**

Results: **The prevalence of any positive skin prick test (SPT) in ADHD patients was higher than the control, 67.5% and 45.0%, respectively. (p =0.043) The five most common sensitizing allergens were as follows: *D. farinae*, 42.5 %, *D. pteronyssinus* 40.0%, Bermuda grass 37.5%, American cockroach 35.0%, German cockroach 30.0% and Johnson grass 30.0% in ADHD children *D. farinae* 32.5 %, *D. pteronyssinus*, 32.5%, German cockroach 22.5%, American cockroach 20.0% and Bermuda grass 20.0% in control children. No significant differences were detected between the groups on type of allergen except Johnson grass. Sensitization to Johnson grass was significantly higher in the ADHD group, 30.0% in ADHD cases and 10.0% in control cases. (p = 0.048) The frequency of allergic rhinitis was higher in the ADHD group. (p =0.008) No differences between groups were observed regarding other allergic diseases, asthma, eczema, allergic conjunctivitis, food allergy and urticaria. (p > 0.05)**

Conclusions: **Our results suggest that there were increased rates of allergic sensitization and allergic rhinitis in ADHD children. Therefore, assessment of allergic sensitization may be beneficial in children diagnosed with ADHD. *(Asian Pac J Allergy Immunol 2011;29:57-65)***

Key words: *attention deficit hyperactivity disorder, allergic disease, allergic sensitization, atopy, skin prick test*

Abbreviations:
ADHD = attention deficit hyperactivity disorder
SPT = Skin prick test

Introduction

Despite significant advances in prevention and treatment, allergic diseases (asthma, eczema and allergic rhinoconjunctivitis) in childhood represent a major and increasing health problem worldwide,[1] including Thailand.[2] The development of atopic disease depends on a complex interaction between genetic and several environmental factors such as environmental exposure to food and inhalant allergens, and non-specific adjuvant factors, e.g., air pollution and tobacco smoke.[3] It is unlikely that a change in genetic factors can explain the increased prevalence of asthma and allergy seen during the

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last decades. It is evident that environmental factors play a major role in the development of sensitization and allergic disease, and that many different environmental factors may contribute to the increase in the prevalence of the allergic diseases.[4] Allergen exposure leads to sensitization and that sensitization is an important risk factor for the development of allergic disease, but the exact relationship between allergen exposure and the development of allergic disease is unclear.[5]

Attention deficit hyperactivity disorder (ADHD) is also a common chronic disease in the pediatric population, with an estimated prevalence in school-aged children of 6.8% with a three-fold higher rate in boys than in girls. It is recognized by difficulties with attention, impulsivity and hyperactivity.[6] ADHD is a genetically complex disorder and interaction between genetic makeup and the environment correlation and developmental factors are important.[7] According to family and twin studies, genes have a substantial role in the familial transmission of ADHD.[8] Environmental influences like fetal distress, hypoxia and family dysfunction are considered to have etiological importance.[8] The dopaminergic system, noradrenergic and histaminergic systems can be involved with ADHD.[9] This supports the hypothesis that the pathophysiology of ADHD involves the neuroendocrine-immunological network.

ADHD and allergic disorders are both hereditary diseases involving gene-environment interactions that may share a common biological background. Children with allergic diseases such as eczema, asthma and allergic rhinitis may also exhibit hyperactive and impulsive behavior, which has been thought to be secondary to chronic illness or to its treatments. ADHD symptoms after eating normal amounts of certain food or artificial colors or a sodium benzoate preservative[10-11], or after pollen exposure[12], could be due to hypersensitivity. If hypersensitivity to environmental stimuli like foods or aeroallergens contributes to the development of ADHD, the evaluation and treatment of ADHD will have to be reconsidered. These children may require combined and integrated medical diagnostic, prevention and treatment strategies. This new insight will improve the quality of care for ADHD patients and consequently reduce the use of medication in the future.

Allergic sensitization was defined as the presence of at least one positive skin reaction to any allergen tested. Skin prick test (SPT) reactivity is a valid and useful method for measuring allergic sensitization. The purpose of this study was to determine whether allergic sensitization (positive skin prick test result) and allergic diseases are associated with physician-diagnosed ADHD.

Methods

A case-control study was conducted between January and November 2010 at the Faculty of Medicine, Vajira Hospital, University of Bangkok Metropolis. Forty children, aged 5 to 15 years, with developmental and behavioral pediatrician-diagnosed ADHD who met *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* criteria for ADHD were included in this study.[13] In the control group, non-ADHD children were equal in number and were recruited from outpatients. They were individually matched for sex and age, within 12 months, from well baby and dental clinics and from the department for minor surgical procedures during the same period. Children with psychotic disorders, schizophrenia or pervasive developmental disorder were excluded from this study. The study protocol was approved by the Ethics Committee on Research Involving Human Subjects of the institution and the Bangkok Metropolitan Administration Committee before commencement of the study. After informed consent was obtained from the parents and also from the patients when appropriate, demographic and home environmental characteristics of the subjects were recorded. All patients were evaluated for eczema, asthma, allergic rhinitis, allergic conjunctivitis, urticaria and food allergy by history and physical examination. They underwent skin prick tests for common inhaled and food allergens for Thailand using ALK-Abello diagnostic extracts (Port Washington, New York). SPTs for 22 common allergens were used: Bermuda grass, Johnson grass, acacia, cat dander, dog dander, house dust mite: *Dermatophagoides pteronyssinus (Dp)*and *Dermatophagoides farinae (Df)*, American cockroach, German cockroach, kapok, alternaria, cladosporium, aspergillus mix, egg white, egg yolk, cow's milk, soybean, wheat, peanut, mixed fish, mixed shell fish and shrimp, along with positive control (histamine) and negative control (vehicle). A wheal diameter at least 3 mm greater

Table 1. Comparison of the characteristics between ADHD patients and control group

Characteristics	ADHD cases N=40	Non-ADHD Controls N=40	*p* value
Age, year, mean (SD)	9.1 (2.1)	9.0 (2.3)	0.780 [c]
Male, no (%)	31 (77.5)	31 (77.5)	1.000 [a]
BMI, kg/m^2, mean (SD)	18.4 (4.2)	16.8 (3.4)	0.070 [c]
No siblings, no (%)	16 (40.0)	18 (45.0)	0.651 [a]
Family history (parent or sibling) of allergy, no (%)	14 (35.0)	17 (42.5)	0.491 [a]
Family suggest hyperactive, no (%)	12 (30.0)	0 (0)	< 0.001 [a]
Household income (baht/month), no (%)			0.496 [a] *
<10,000	8 (20.0)	2 (5.0)	
10,000-30,000	14 (35.0)	23 (57.5)	
30,000-50,000	16 (40.0)	12 (30.0)	
>50,000	2 (5.0)	3 (7.5)	
Caregiver, no (%)			0.034 [a]**
Father	1 (2.5)	7 (17.5)	
Mother	25 (62.5)	28 (70.0)	
Grandfather	3 (7.5)	1 (2.5)	
Grandmother	10 (25.0)	2 (5.0)	
Aunt	1 (2.5)	2 (5.0)	
Education of caregiver, no (%)			0.369 [a]
> High school	20 (50.0)	16 (40.0)	
≤ High school	20 (50.0)	24 (60.0)	
Prenatal, no (%)			
Maternal smoking	3 (7.5)	0 (0)	0.241 [b]
Exposure to smoking environment	23 (57.5)	18 (45.0)	0.263 [a]
Alcohol abuse or dependence during pregnancy	7 (17.5)	0 (0)	0.012 [b]
Natal			
Preterm, no (%)	3(7.5)	0(0)	0.241 [b]
Birth weight, gram, mean (SD)	3067.7(500.3)	3189.2(466.2)	0.268 [c]
Postnatal, no (%)			
Breast-feeding at least 4 months	11 (27.5)	12 (30.0)	0.805 [a]
Head injury	6 (15.0)	0 (0)	0.026 [b]
Urban residence	36 (90.0)	32 (80.0)	0.348 [a]
Exposure to tobacco smoke at home	15 (37.5)	17 (42.5)	0.648 [a]
Owning pets (dogs or cats)	14 (35.0)	13 (32.5)	0.813 [a]

BMI, body mass index SD, standard deviation

a: *p* value by Chi-square test; b: *p* value by Fisher's exact test; c: *p* value by independent t-test

*compared with household income less than or 30,000 and more than 30,000 baht/month

** compared with caregiver as father or mother and others

than the negative control was interpreted as positive, evaluated after ten minutes for histamine and 15 minutes for allergens.[14] The patients had not taken any antihistaminic drugs within ten days prior to skin testing, as recommended prior to and verified on the day of testing.

Statistical analysis

Continuous data were described with mean and standard deviation values, while the categorical data were investigated by frequency and percentages. Independent t-test or Mann Whitney U-test was used to analyze continuous variables depending on data distribution. Frequencies of demographic data, allergic sensitization (positive skin prick test result) and allergic diseases between the two groups were compared using chi-squared tests or Fisher's exact test. A p value of less than 0.05 was considered statistically significant (two-tailed test). Association between allergic sensitization or allergic diseases and ADHD were analyzed by multivariate analysis (adjusted analysis) using backward stepwise multiple logistic regression analyses for "adjusted odds ratio" (OR) and 95% confidence intervals (CI).

Results

A total of 40 ADHD and 40 non-ADHD control subjects were enrolled in the study. The control group was matched for age and sex; 30 of them were recruited from a dental clinic or well baby clinic for routine vaccination, while the remaining ten attended the department for minor surgical procedures, e.g., extirpation of a nevus. The mean age of the participants was 9.0 ± 2.2 years, mean age was 9.1 ± 2.1 years for the ADHD group (31 males, 9 females) and 9.0 ± 2.3 years for the control group (31 males, 9 females). Males comprised 77.5% of child participants. The ratios between boys and girls were 3.4:1 in both groups. No difference in sex and age between both groups was found. In the ADHD group, the mean age of diagnosis of ADHD was 6.8 ± 1.5 years (range 5.0 to 10.6 years) with a mean treatment duration of 2.4 ± 1.7 years (range 0 to 6.1 years). The primary caregiver for 80 participants was commonly the mother (66.3%), but occasionally the father (10.0%), grandmother (15.0%), grandfather (5.0%) or aunt (3.7%). The father or mother was a primary caregiver for the control group which was significantly higher than the ADHD group (p =0.034). Both groups did not differ with respect to caregiver education and/or household income. There was no reported family history of previous ADHD or hyperactivity/inattention in the control group, whereas 30% (father 7.5%, mother 5%, sister 7.5%, brother 5.0% and aunt 5.0%) had such

Table 2. Sensitizing allergens in ADHD cases and control cases

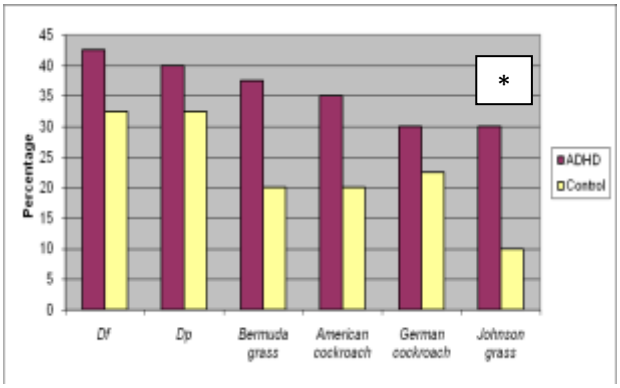
	Total (n=80) Number (%)	ADHD cases (n=40) Number (%)	Non-ADHD control (n=40) Number (%)	*p* value
SPT positive	45 (56.3)	27 (67.5)	18 (45.0)	0.043 [a]
Aeroallergens	45 (56.3)	27 (67.5)	18 (45.0)	0.043 [a]
Df	30 (37.5)	17 (42.5)	13 (32.5)	0.356 [a]
Dp	29 (36.3)	16 (40.0)	13 (32.5)	0.485 [a]
Bermuda grass	23 (28.8)	15 (37.5)	8 (20.0)	0.084 [a]
American cockroach	22 (27.5)	14 (35.0)	8 (20.0)	0.133 [a]
German cockroach	21 (26.3)	12 (30.0)	9 (22.5)	0.446 [a]
Johnson grass	16 (20.0)	12 (30.0)	4 (10.0)	0.048 [b]
Dog dander	13 (16.3)	9 (22.5)	4 (10.0)	0.225 [b]
Kapok	9 (11.3)	5 (12.5)	4 (10.0)	1.000 [b]
Acacia	8 (10.0)	7 (17.5)	1 (2.5)	0.057 [b]
Cladosporium	7 (8.8)	6 (15.0)	1 (2.5)	0.108 [b]
Aspergillus mix	5 (6.3)	4 (10.0)	1 (2.5)	0.359 [b]
Alternaria	4 (5.0)	3 (7.5)	1 (2.5)	0.615 [b]
Cat dander	2 (2.5)	2 (5.0)	0 (0)	0.494 [b]
Food allergens	25 (31.3)	15 (37.5)	10 (25.0)	0.228 [a]
Shrimp	12 (15.0)	8 (20.0)	4 (10.0)	0.348 [b]
Mixed shell fish	10 (12.5)	8 (20.0)	2 (5.0)	0.087 [b]
Egg white	9 (11.3)	3 (7.5)	6 (15.0)	0.481 [b]
Soybean	6 (7.5)	5 (12.5)	1 (2.5)	0.201 [b]
Cow's milk	5 (6.3)	3 (7.5)	2 (5.0)	1.000 [b]
Mixed fish	5 (6.3)	4 (10.0)	1 (2.5)	0.359 [b]
Wheat	3 (3.8)	3 (7.5)	0 (0)	0.241 [b]
Peanut	3 (3.8)	3 (7.5)	0 (0)	0.241 [b]
Egg yolk	2 (2.5)	1 (2.5)	1(2.5)	1.000 [b]

Df = Dermatophagoides farinae

Dp= Dermatophagoides pteronyssimus

a: *p* value by Chi-square test; b: *p* value by Fisher's exact test

a history in the ADHD group. (p <0.001) Two ADHD patients' sisters were diagnosed with autism; however, no significant difference among the groups was observed. (p = 0.494) The children with ADHD demonstrated a higher occurrence of perinatal risk factors: preterm, maternal smoking, exposure to smoking environment and alcohol drinking during pregnancy, but the difference was statistically significant only for alcohol drinking during pregnancy factor (p =0.012). The children with ADHD had a significantly higher past history of head injury, either admitted to a hospital or investigated, i.e., computed tomography (CT). (p =0.026)



Df = Dermatophagoides farinae

Dp= Dermatophagoides pteronyssinus

ADHD, attention deficit hyperactivity disorder

Figure 1. The ADHD cases were more likely to have positive skin prick tests to each allergen than control, but the significant associations were detected only in Johnson grass sensitization (*, $p < 0.05$).

Evaluation for allergic symptoms indicated familial atopy (first-degree family member) in 35.0% of ADHD children and 42.5% of control children (p =0.491). The groups did not differ significantly in terms of life environmental factors likely to affect allergic state: no siblings, breast feeding at least four months, exposure to tobacco smoke at home, area of residence and owning pets. Demographic characteristics are shown in Table 1.

Table 2 shows the types of allergen responses for both groups. Skin prick testing was performed on all patients. Forty-five (56.3%) cases were atopic, defined by having at least one positive skin-prick-test. Twenty-seven patients (67.5%) were skin test positive in the ADHD group whereas 18 patients (45.0%) tested positive in the control group. This difference in the skin test positive rates between the ADHD group and control group was significant (p =0.043). The six most common sensitizing allergens were *Df* (42.5%), followed by *Dp* (40.0%), Bermuda grass (37.5%), American cockroach (35.0%), German cockroach (30.0%) and Johnson grass (30.0%) in ADHD cases and *Df* (32.5%), *Dp* (32.5%), followed by German cockroach (22.5%), Bermuda grass (20.0%), American cockroach (20.0%) and egg white (15.0%) in the control cases. The ADHD cases were more likely to have positive skin prick tests to each allergen than the control, but significant associations were observed only in Johnson grass sensitization (p =0.048) (Figure 1.). House dust mites (*Df*, *Dp*) were the

most common sensitizing allergens in both groups.Of 20 ADHD children (50.0%) who were sensitized to dust mite allergens, 13 were sensitized to both *Df* and *Dp*, whereas only 4 and 3 children were sensitized to *Df* or *Dp* alone, respectively. Of the 13 control children (32.5%) were sensitized to dust mite allergens and all of these patients were sensitized to both *Df* and *Dp*. A positive SPT to cat was uncommon in this study. None of the control group was sensitized to this allergen. Sensitivity to aeroallergen and food allergen was found as 67.5% and 37.5%, respectively, in ADHD children, and 45.0% and 25.0%, respectively, in control children. No significant differences were detected between the groups with regard to food allergens (p =0.228), but a difference in aeroallergens was observed (p = 0.043). For patients with at least one positive skin test result, 17 (63%) of the 27 patients in the ADHD group and 9 (50.0%) of the 18 patients in the control group were diagnosed with allergic diseases. No significant differences were detected between the groups (p =0.388). The number of positive tests among children in the ADHD and the control group, indicated that the numbers of children in the atopic ADHD group with 1, 2, 3, 4, 5 or more sensitizing allergens were 1, 6, 3, 4 and 13 children, respectively, whereas 3, 2, 1, 3 and 9 children, respectively, were observed in the atopic control. No differences were observed between positive rates in the skin test less than 5 or ≥5 allergens between the ADHD and control groups (p =0.903).

Twenty-six (65%) ADHD patients had associated allergic diseases: 5 patients with eczema (12.5%), 6 patients with asthma (15.0%), 24 patients with allergic rhinitis (60.0%), 9 patients with allergic conjunctivitis (22.5%), 1 patient with urticaria (2.5%), 2 patients with food allergy (5.0%). Of the controls,15 (37.5%) had allergic disease: 4 patients with eczema (10.0%), 5 patients with asthma (12.5%), 13 patients with allergic rhinitis (32.5%), 4 patients with allergic conjunctivitis (10.0%), 5 patients with urticaria (12.5%), and 3 patients with food allergy (7.5%). Asthma severity was classified using GINA criteria in place at the time of data collection (The Global Initiative for Asthma, 2006).[15] Using this method, 72.7% of the asthma cases were classified as mild intermittent, 9.1% mild persistent and 18.2% moderate persistent. None of participants was classified as severe persistent. Using ARIA (Allergic Rhinitis and its impact on Asthma) classification[16], allergic rhinitis disease severity was classified as 48.6% mild intermittent, 18.9% mild persistent, 8.1% moderate-severe persistent, and 24.4% moderate-severe intermittent. No significant differences were observed between the groups with regard to the severity of asthma and allergic rhinitis (p > 0.05) (Table 3).

Table 3. Number and percentage of allergic diseases in attention-deficit hyperactivity disorder (ADHD) patients and their matched controls

Allergic diseases*	ADHD cases (n=40)	Non-ADHD Controls (n=40)	p value
Allergic diseases, no (%)	26 (65.0)	15 (37.5)	0.014 [a]
Eczema, no (%)	5 (12.5)	4 (10.0)	1.000 [b]
Asthma, no (%)	6 (15.0)	5 (12.5)	0.745 [b]
Mild intermittent	4 (10.0)	4 (10.0)	1.000 [b]
Mild persistent	0 (0)	1 (2.5)	1.000 [b]
Moderate persistent	2 (5.0)	0 (0)	0.152 [b]
Severe persistent	0 (0)	0 (0)	
Allergic rhinitis, no (%)	24 (60.0)	13 (32.5)	0.014 [a]
Mild intermittent	12 (30.0)	6 (15.0)	0.108 [a]
Mild persistent	6 (15.0)	1 (2.5)	0.108 [b]
Moderate-severe intermittent	1 (2.5)	2 (5.0)	1.000 [b]
Moderate-severe persistent	5 (12.5)	4 (10.0)	1.000 [b]
Allergic conjunctivitis, no (%)	9 (22.5)	4 (10.0)	0.225 [b]
Urticaria, no (%)	1 (2.5)	5 (12.5)	0.201 [b]
Food allergy, no (%)	2 (5.0)	3 (7.5)	1.000 [b]

*Some participants had more than 1 disease.
a: p value by Chi-square test; b: p value by Fisher's exact test

Multivariable analysis showed that the association between ADHD and allergic sensitization (67.5% in the ADHD group vs. 45.0% in the control group, adjusted OR, 2.59; 95% CI, 1.02 to 6.56; p =0.045), ADHD and positive SPT to aeroallergens (67.5% in the ADHD group vs. 45.0% in the control group, adjusted OR, 2.59; 95% CI, 1.02 to 6.56; p =0.045), ADHD and allergic diseases, as defined by the presence of at least one diagnosed allergic disease (65% in the ADHD group vs. 37.5% in the control group, adjusted OR, 3.84; 95% CI, 1.42 to 10.42; p =0.008) ADHD and allergic rhinitis (60.0% in the ADHD group vs. 32.5% in the control group, adjusted OR, 3.80; 95% CI, 1.41 to 10.26; p =0.008) were independent of other variables, such as no siblings, family history of allergy and breast-feeding for at least four months. Other allergic comorbidities were not significantly associated with ADHD (eczema adjusted OR, 1.18; 95% CI, 0.27 to 5.03; p =0.828; asthma adjusted OR, 1.37; 95% CI, 0.35 to 5.33; p =0.650; allergic

conjunctivitis adjusted OR, 3.01; 95% CI, 0.81 to 11.27; *p* =0.101; urticaria adjusted OR, 0.22; 95% CI, 0.03 to 2.10; *p* =0.189; and food allergy adjusted OR, 0.93; 95% CI, 0.14 to 6.34; *p* =0.937). However, children with ADHD tended to have a higher prevalence of eczema, asthma and allergic conjunctivitis (Table 4).

Table 4. Adjusted odds ratios of allergic sensitization and allergic diseases of ADHD children and control

Comorbidities	Adjusted odds ratio (95% CI)	*P* -value
Allergic sensitization	2.59 (1.02-6.56)	0.045
Positive to aeroallergen	2.59 (1.02-6.56)	0.045
Positive to food allergen	1.76 (0.66-4.69)	0.261
Allergic diseases	3.84 (1.42-10.42)	0.008
Eczema	1.18 (0.27-5.03)	0.828
Asthma	1.37 (0.35-5.33)	0.650
Allergic rhinitis	3.80 (1.41-10.26)	0.008
Allergic conjunctivitis	3.01 (0.81-11.27)	0.101
Urticaria	0.22 (0.03-2.10)	0.189
Food allergy	0.93 (0.14-6.34)	0.937

Discussion

The purpose of this study was to investigate the possible relationship between allergic sensitization, which is an increased risk of developing allergic diseases and ADHD. The male-to-female ratio for this study was 3.4:1. Our study affirmed that the male sex is associated with a raised prevalence of ADHD.[6] A family history of ADHD and alcohol abuse during pregnancy were significantly associated with physician-diagnosed ADHD. Maternal smoking and exposure to smoking environment during pregnancy were higher in ADHD patients; however, none of these associations reached statistical significance. Previous studies found that prenatal exposure to maternal tobacco smoking and alcohol were risk factors for ADHD.[17] This may be because nicotinic receptors modulate dopaminergic activity and dopaminergic dysregulation could cause ADHD. A family history of hyperactivity is more common in children with hyperactivity and those diagnosed with ADHD. Thus, our study confirmed that genetic predisposition is an important risk factor for ADHD. Moreover, we found that a history of head injury was significantly associated with increased risk of diagnosed ADHD. Ebaugh et al. noted behavior disorders, including attention deficit and hyperkinesis, after acute epidemic encephalitis and cerebral trauma in children.[18-19]

Gender is associated with allergic sensitization and allergic diseases, i.e., males are more frequently affected; thus, this study was designed to match sex and age.[20] A family history of allergy and urban living were positively associated with allergic sensitization but breast-feeding for at least four months and having several siblings was noted to be negatively associated with allergic sensitization.[21] However, no significant differences were noted between the two groups.

In this study, the prevalence of allergic sensitization among the ADHD patients was 67.5%, consistent with a previous study reporting 61%,[22] whereas allergic sensitization in the control group was 45.0%, higher than a previous study which reported 35.2%.[23] Males comprised 77.5% of the children. The prevalence of any positive SPT in males was higher than in females[20] and this may explain why allergic sensitization in the control group was quite high. Surprisingly, the prevalence of allergic sensitization among ADHD children was similar to the rates reported in asthmatic children in Thailand (64.3%). Moreover, it was higher than for asthmatic adult (43.7%).[23] The most common allergens causing sensitization in both groups were *Df* and *Dp*. This result supports the finding from previous studies that house dust mites are the most important allergens in Thailand.[23] None of the patients in the control group was sensitized to cat dander. The frequency of families with atopic diseases was higher in the control group. Thus, parents should be concerned about the development of allergic disease in their children and pets may need to be avoided. However, the association between exposure to pets and subsequent development of sensitization and allergic disease remains controversial. It is surprising that the rate of sensitization to Johnson grass among ADHD children was significantly higher than the control children. Sensitization of aeroallergens was higher than for food allergens in both groups. In agreement with previous studies, food allergen sensitization was most prevalent during the first years of life, diminishing in prevalence in later childhood. Conversely, the risk of sensitization to aeroallergens increases with age throughout childhood.[24] A family history of allergy was higher in the control cases but not in a way that corresponded to the increase in

allergic sensitization in their children, suggesting that the increase probably is related to environment or lifestyle rather than changed genetic predisposition.

The high prevalence of allergic diseases among our subjects could be due to the fact that most participants (80 to 90%) lived in urban areas. The prevalence of allergic diseases in Bangkok, the capital city in Thailand, was slightly higher than others such as Chiang Mai, Northern Thailand.[2] The most common allergic diseases in this study was allergic rhinitis. It may be explained by 'allergic march', a developmental pattern for a cluster of allergic diseases that begins in early childhood. Eczema and certain food allergies tend to be outgrown or improve during the preschool years. In comparison, asthma and allergic rhinitis tend to declare themselves later, becoming increasingly common beginning at approximately three to four years and continuing into the school-age years. Most of the participants were school age children. ADHD cases were 2.6 times more likely to have been sensitized to aeroallergen and 3.8 times more likely to have been diagnosed with allergic rhinitis than were the non-ADHD control subjects. These results confirm the importance of aeroallergens as they are directly correlated with the presence of allergic rhinitis. Our study showed a significant increase in sensitization to common allergens in ADHD patients. This result supported those of the previous study by Brawley et al.[22], who found that most patients with ADHD had symptoms and skin prick test findings to common aeroallergens which were consistent with a diagnosis of allergic rhinitis. The prevalence of asthma among the allergic rhinitis patients was 23.1% in the control group and 16.7% in the ADHD group, consistent with those in previous studies ranging between 7.6 and 22.6%.[25] No significant differences were found between the two groups (p =0.678). The prevalence of allergic rhinitis among the asthma patients was 100% in both groups, higher than previous studies which have reported rates ranging from 78to 81%.[25] ADHD patients in this study were also more likely to be diagnosed with eczema, asthma and allergic conjunctivitis. However, no significant differences were observed between the groups. These findings may be explained by the small sample size in this study. Conflicting data exist in the literature regarding the relationship between ADHD and allergic diseases. Schmitt J et al.[26] reported a significant association of ADHD and atopic eczema in a large population-based sample. Romanos et al.[27] described children with atopic eczema and concomitant sleep disturbance have a more than 2.5-fold increased risk of being diagnosed as having ADHD. Recently, a systematic review study[28] found that children with eczema and children with asthma are more frequently diagnosed as having ADHD than children without these chronic diseases. The previous study [29] suggested that food allergy and food additives were a possible mechanism underlying the hyperkinetic syndrome. The underlying mechanisms of an adverse food reaction could be based on allergic sensitization, resulting in immunoglobulin E (IgE) or non-IgE-mediated mechanisms, or on non-allergic mechanisms. No differences between the groups were observed regarding the diagnosis of food allergy or positive SPTs to food allergens. We evaluated only IgE-mediated food allergy. Thus our findings do not exclude a non-IgE mediated mechanism. In contrast to these findings, the results a study by Gaitens et al. [30] and McGee et al. [31] did not support an association between parents, teachers, and self-reports of ADHD behavior and atopic disorders, based on IgE-mediated atopic responsiveness. However the in most of the studies reported the criteria to define atopic disease and ADHD were inadequate because of the diagnosis of ADHD and allergic diseases according to parental reports or on secondary data from routine practice. The lack of validity and reliability of diagnoses may limit the interpretation of the results. The strength of this study, based on *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* criteria, is that ADHD cases were diagnosed by developmental and behavioral pediatricians and all patients were diagnosed with allergic diseases and the skin prick tests were performed by an allergist. Nevertheless, a limitation of our study was that the control cases were not randomly selected but were those who agreed to participate in this study. However, the prevalence of allergic diseases in the control group could be similar the Thai general population.[2] Furthermore, subjects enrolled from one urban hospital and evaluation in other sites and populations would be helpful to confirm these findings.

The results of this study provide support for the hypothesized relationship between allergic sensitization and allergic rhinitis in childhood and ADHD. The reasons that allergic sensitization or allergic rhinitis may affect the development of ADHD later in life remain unclear. These findings may be explained in two ways. Firstly, the children with allergic sensitization are exposed to increased levels of proinflammatory cytokines and mediators released during the atopic response that may pass the blood brain barrier[32] and activate neuroimmune mechanisms that involve behaviorally and emotionally relevant circuits.[33] Secondly, the prefrontal cortex is known to subserve executive cognitive functions such as planned behavior, decision making, motivation and attention, [34] which is activated during an atopic episode.[35] A previous immunological study found dopamine transporters are causally implicated in ADHD, and are targets for drugs like methylphenidate. These receptors are abundantly expressed on human T-cells and trigger the selective secretion of immune-regulatory cytokines, like interleukin (IL)-10 and react by activating STAT6, a transcription factor in Th2 cells of the immune system.[36-37]

Our study confirms that ADHD is a multifactorial and heterogeneous disorder which is familial and inherited . ADHD and allergic diseases may share common etiological (genetic or environmental or both) pathways. Children with this condition may require combined and integrated medical diagnostic, prevention and treatment strategies. A better understanding of the association between allergic sensitization, allergic diseases and the development of ADHD may lead to targeted preventions, treatments and improved quality of life for those children.

In summary, we report increased rates of allergic sensitization in ADHD cases. Children with ADHD also had an increased prevalence of allergic rhinitis. ADHD children, especially the ones who have symptoms of allergic diseases, should be considered for evaluation of possible allergic sensitization for prevention, avoidance of allergens and treatment. Although no increase in symptoms of other allergic diseases in ADHD cases was observed, the increase in sensitization may predict a continuous increase in clinical manifestations of allergic diseases in the future. Thus, they should be closely followed.

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