



Association between atopic diseases and attention-deficit/hyperactivity disorder in childhood: a population-based case-control study

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ARTICLE INFO

Article history:

Received 11 August 2012

Accepted 24 December 2012

Keywords:

Atopic disease

ADHD

Childhood

Health insurance database

Taiwan

Purpose: Both atopic diseases (AD) and attention-deficit/hyperactivity disorders (ADHD) are common pediatric disorders that may lead to mental and physical complications. This population-based, case-control design is to correlate the risk of ADHD with AD among a pediatric population.

Methods: By using a Longitudinal Health Insurance Database ranged from 2002 to 2009, 4692 children with ADHD and 18,768 randomly selected controls were enrolled. Odds ratios (OR) of ADHD were calculated for the association with AD.

Results: The children with ADHD had a higher rate of AD than controls, particularly allergic rhinitis and allergic conjunctivitis. The corresponding ORs were 1.81 (95% confidence interval [CI], 1.69–1.93) and 1.69 (95% CI, 1.58–1.81), respectively. Despite the lower prevalence, children with atopic dermatitis and asthma were also at higher risk of ADHD, with ORs of 1.80 (95% CI, 1.58–2.05) and 1.48 (95% CI, 1.24–1.78). Logistic regression analysis estimated ORs showed ADHD risk was higher for those living in urban areas. The risk of ADHD increased with numbers of AD and age.

Conclusions: Most of the children with ADHD had a strong association with AD, especially allergic rhinitis. Awareness of these comorbidities may help clinicians to provide better comprehensive management and reduce the burden of disease.

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Introduction

Atopic diseases (AD) are common chronic conditions encountered in pediatric clinics. They usually manifest as recurring, noninfectious, inflammatory conditions, and cause a large economic burden despite the development of prevention therapies and medication [1–4]. It is evident that environmental factors play a role in the development, and the prevalence of allergic diseases depends on complex interactions between genetic and environmental factors [5]. Numerous complications can lead to significant problems both physically and mentally in childhood, and subsequent substantial behavioral disorders can lead to psychosocial impairment [6].

Epidemiologic studies have documented that attention-deficit/hyperactivity disorder (ADHD) is a common neurobehavioral disorder in pediatric populations, and estimated a prevalence rate of 5% in school-aged children, with a 3- to 4-fold higher rate in males than females [7]. The characteristics are recognized by behavioral symptoms of inattention, impulsivity, and hyperactivity [8]. Variable environmental influences are known to raise the risk of ADHD development. The etiologies are multifactorial, and interactions between genetic and environmental factors have been suggested to cause this disorder [9].

Both AD and ADHD are hereditary diseases involving gene–environment interactions. Previous research has shown an epidemiologic correlation and substantial pathophysiologic relationship between AD and ADHD in childhood [10–12]. Children with AD may exhibit hyperactivity and impulsive behavior that may be thought to be secondary to the illness [13]. AD and ADHD are frequent and highly impairing childhood conditions imposing a substantial financial burden on social services. The purpose of this study was to examine the relationship between AD and ADHD using a population-based, case-control study, with the hypothesis that AD may be a potential cause or exacerbating factor of ADHD symptoms.

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Methods

Data source

We used the Longitudinal Health Insurance Database (LHID), established by the National Health Research Institutes, Department of Health, Taiwan, for this study. This database includes claims data from 1996 to 2009 for 1 million people covered in the Taiwan National Health Insurance program. There were no differences in the distributions of gender and age between the LHID and all beneficiaries. The Taiwan National Health Insurance system was launched in March 1995, with 23.03 million (99.2%) of the population and 91% medical institutions of Taiwan insured by the end of 2009 (<http://www.doh.gov.tw>). Information on the basic patient demographics and medical care received, including outpatient and inpatient claims, dental care, childbirth, physical therapy, preventive care, home care, and rehabilitation, are available. The National Health Research Institutes provide 18 National Health Insurance Research Databases to Taiwanese scientists for research. We were able to link the LHID with the other datasets using scrambled patient identification numbers to secure the privacy of individuals. The present study was thus exempted from ethical review. The *International Classification of Diseases, 9th Revision, Clinical Modification* (ICD-9-CM) was used to identify diagnoses of diseases in the claims data because of government policy.

Study sample

We identified 4692 children (<18 years old) with ADHD (ICD-9-CM code 314) from 2002 to 2009 with the date of diagnosis as the index date. The diagnosis of ADHD was based on at least two outpatient department visits with the diagnosis of ADHD in the primary coding field. Diagnostic criteria of ADHD based on the *Diagnostic and Statistical Manual of Mental Disorders, fourth edition*, and assessment of ADHD or AD were made by clinical physicians in charge at medical institutions. Four control children were randomly selected for each ADHD case, matched for age, gender, index year, and index month (in total, 18,768 controls). None of the controls had a history of ADHD. Information on ADHD, AD, and urbanization level of where the study subjects resided were also extracted for this study. The urbanization of Taiwan is divided into seven levels according to the National Health Research Institutes, with level 1 being the most urbanized area and level 7 the least. In this study, we combined urbanization levels 5 through 7 into level 5 because of the small number of cases in these levels. The AD included allergic conjunctivitis (ICD-9-CM codes 372.05, 372.10 and 372.14), allergic rhinitis (ICD-9-CM code 477), asthma (ICD-9-CM codes 493.00–493.12), and atopic dermatitis (ICD-9-CM code 691.8), identified before the index date and during at least three medical visits with diagnosis appeared in either primary or secondary coding fields. For protection of privacy, the identities of patients, physicians, and institutions were scrambled in accordance with the Personal Electronic Data Protection Law.

Statistical analysis

The chi square test was used to assess differences of categorical variables between the ADHD and non-ADHD groups. Unconditional logistic regression was used to estimate the odds ratios (ORs) and 95% confidence intervals (95% CI) for the association between AD and ADHD, controlling for urbanization. We further estimated the risk of ADHD associated with the number of AD by gender controlling for age (<7, 7–12, and 12–18 years) and urbanization,

and by age controlling for gender and urbanization. All statistical analyses were performed using SAS software version 9.1 (SAS Institute Inc., Cary, NC), and the significance level was set at .05 in two-tailed tests.

Results

Table 1 shows a comparison of the gender, age, urbanization and AD between the ADHD and non-ADHD groups. There were no differences in demographics between the two groups. The study consisted of 4692 children with ADHD and 18,768 matched controls (77.9% male), with a mean age of 8.91 years (SD, 3.02); 70.1% of the subjects were 7 to 12 years of age. Most of the children lived in urban areas (66.4%). The ORs of those with ADHD were reduced in less urbanized areas. As a result, the risk for ADHD is significantly associated with AD, particular allergic rhinitis (46.3% vs. 32.3%) and allergic conjunctivitis (33.7% vs. 23.1%). The risk of ADHD increased for children with allergic rhinitis (OR, 1.81; 95% CI, 1.69–1.93), atopic dermatitis (OR, 1.80; 95% CI, 1.58–2.05), allergic conjunctivitis (OR, 1.69; 95% CI, 1.58–1.81), and asthma (OR, 1.48; 95% CI, 1.24–1.78) in the univariate logistic regression analysis. Most of the children had an allergic disease diagnosed 20 to 80 months before the diagnosis of ADHD (Fig. 1).

When the association between AD and ADHD was evaluated by gender, the adjusted risk for both genders was significantly related to allergic rhinitis, allergic conjunctivitis, and atopic dermatitis. The ORs increased with the number of allergic diseases, to 3.87 (95% CI, 2.57–5.83) for girls and 2.58 (95% CI, 2.10–3.15) for boys in those with three AD (Table 2) in multivariable logistic regression. In age-stratified analysis, there was a significant trend between ADHD and age (Table 3). The results suggested a strong association between allergic rhinitis and atopic dermatitis and ADHD in each age group. Significant associations were found in allergic conjunctivitis in those aged 7 to 18 years (Table 3). The adjusted ORs of ADHD increased to 2.63 (95% CI, 1.03–6.74), 2.85 (95% CI, 2.33–3.5), and 2.75 (95% CI, 1.78–4.23) in each age group of those with three or more allergic diseases (Table 3).

Table 1

Comparison of demographic status and atopic diseases between the attention-deficit/hyperactivity disorder (ADHD) and non-ADHD groups with odds ratios (ORs) measured in univariate logistic regression analysis

	Non-ADHD (n = 18,768)		ADHD (n = 4692)		OR	95% CI
	n	%	n	%		
Gender						
Female	4140	22.1	1035	22.1	1.00	Reference
Male	14,628	77.9	3657	77.9	1.00	0.93–1.08
Age (yrs)						
<7	1300	6.9	325	6.9	1.00	Reference
7–12	13,152	70.1	3288	70.1	1.00	0.88–1.14
12–18	4316	23.0	1079	23.0	1.00	0.87–1.15
Mean (SD)		8.93 (3.03)		8.91 (3.02)	1.00	0.99–1.01
Urbanization*						
1	5077	27.1	1655	35.3	1.00	Reference
2	5574	29.7	1461	31.1	.80	0.74–0.87†
3	3707	19.8	856	18.2	.71	0.65–0.78†
4	2614	13.9	472	10.1	.55	0.50–0.62†
5	1795	9.6	248	5.3	.42	0.37–0.49†
Atopic diseases*						
Allergic rhinitis	6062	32.3	2172	46.3	1.81	1.69–1.93†
Allergic conjunctivitis	4338	23.1	1580	33.7	1.69	1.58–1.81†
Atopic dermatitis	778	4.2	339	7.2	1.80	1.58–2.05†
Asthma	450	2.4	165	3.5	1.48	1.24–1.78†

CI = confidence interval.

* Chi-square test $P < .0001$.

† $P < .001$.

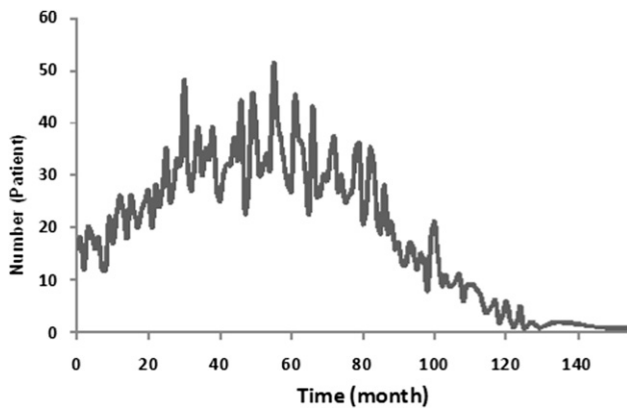


Fig. 1. Distribution of duration between diagnosis of atopic diseases and ADHD.

Discussion

The strength of the present study lies in the nationwide, population-based, case-control database. The large, representative sample of the nationwide database and case-control design suggest high validity and extended availability, and enable us to eliminate various possible coding biases. This results display strong and independent associations between ADHD and AD, adding substantial evidence of the reported relationship [14–16]. The correlations were independent from various factors that are known to have impact on the presence of ADHD, here also demonstrated the association correlated with the numbers of AD even though the severity of the disorders are not available from the LHID database.

The etiologies of both AD and ADHD are multifactorial and heterogeneous, which contributes to their development [9]. The immunopathologic hypothesis is that inflammatory cytokines provoked by allergic reactions activate neuroimmune mechanisms, leading to neurobehavioral disorders, including ADHD [17]. Eventually, ADHD was hypothesized as side effects of allergic reactions engendering cholinergic/adrenergic activity imbalance in the neurologic system [18]. Neuroimmunology research suggests dopamine transporters, abundantly expressed on human T cells, are causally implicated in ADHD and are targets for drug like methylphenidate [19]. As a conclusion, ADHD is hypothesized to be an allergic disorder based on a comparison of mechanisms, and

hypersensitivity to allergens contributes to the development of ADHD [18]. Epidemiology studies had shown an increasing rate of allergies with urbanization [20–22]. Our results also showed that incidence of ADHD are significant than controls in all urbanization level; in contrast, a previous, large, population-based study showed an irrelevant association between urbanization and ADHD with atopic dermatitis [12]. However, the discrepant results of these studies are necessary to define the role of urbanization in ADHD.

Another hypothesis regarding the etiologies is that they share common comorbidities, such as sleep disturbance. Previous studies have explored allergic rhinitis as a risk factor for ADHD; however, it is the most often explored in either population-based studies or laboratory immunization research. It is known to frequently cause sleep disturbance in childhood and to result in poor concentration and distractive behavior; ADHD causes psychological distress and may be a subsequent, exacerbating factor for atopic conditions, although this conclusion is controversial [6,7,9,10]. Children with ADHD had positive skin prick test results to common allergens consistent with allergic rhinitis [11]. It was also suggested that it increased rates of allergic sensitization in a pediatric population [15]. Children with atopic dermatitis have significant sleep problems, which lowers their quality of life. We accounted for potential confounders of the severity and comorbidities subsequent higher levels of ADHD [12,13,23]. Rarely, large studies concern the association of asthma. A population-based twin study showed the influence of genetics; childhood asthma is associated with the subsequent development of hyperactivity in early adolescence [10].

Although ADHD is traditionally assumed to be male predominant, we did not find a significant difference by gender in AD. When adjusted for age, urbanization, and mutual four AD, ADHD was associated with AD, except asthma, for both genders. The confirmatory factor analysis of their study suggested that AD have a significant effect on childhood behavioral disorders [24]. To date, none had reported allergic conjunctivitis to be a risk factor for ADHD.

With regard to the distribution of duration between AD and ADHD, it mostly took 20 to 80 months to diagnose ADHD, which explains why the level of diagnosis of ADHD was lower among preschoolers. It is likely to present from early childhood, and possibly be related to immunity through increased exposure to respiratory infections and subsequent neurobehavioral disorders. The pathophysiology was proposed as allergic rhinitis subsequent

Table 2

Adjusted odds ratios (ORs) of attention-deficit/hyperactivity disorder (ADHD) by gender for association with atopic diseases in multivariate logistic regression

	All		Girls		Boys	
	OR	95% CI	OR	95% CI	OR	95% CI
Atopic diseases*						
Allergic rhinitis	1.59	1.49–1.71 [†]	1.84	1.59–2.13 [†]	1.54	1.42–1.66 [†]
Allergic conjunctivitis	1.43	1.33–1.54 [†]	1.63	1.40–1.91 [†]	1.39	1.28–1.50 [†]
Atopic dermatitis	1.40	1.22–1.61 [†]	1.66	1.25–2.21 [†]	1.33	1.14–1.56 [†]
Asthma	1.15	0.95–1.38	0.88	0.57–1.36	1.22	1.00–1.50
Number of atopic diseases						
0	1.00	Reference	1.00	Reference	1.00	Reference
1	1.63	1.51–1.75 [†]	1.81	1.55–2.11 [†]	1.58	1.45–1.72 [†]
2	2.25	2.06–2.47 [†]	2.88	2.35–3.53 [†]	2.12	1.91–2.34 [†]
≥3	2.79	2.33–3.35 [†]	3.87	2.57–5.83 [†]	2.58	2.10–3.15 [†]
P for trend	<.0001		<.0001		<.0001	

CI = confidence interval.

Adjusted for age, urbanization. The “all” column was adjusted for gender.

* Adjusted for age, urbanization, and mutual four allergic diseases.

[†] P < .001.

Table 3

Adjusted odds ratios (ORs) of attention-deficit/hyperactivity disorder by age for association with atopic diseases in multivariate logistic regression

	Age (yrs)					
	<7 (n = 1625)		7–12 (n = 16,440)		12–18 (n = 5395)	
	OR	95% CI	OR	95% CI	OR	95% CI
Atopic diseases*						
Allergic rhinitis	1.75	1.33–2.30 [†]	1.59	1.47–1.73 [†]	1.59	1.37–1.83 [†]
Allergic conjunctivitis	1.29	0.23–1.81	1.45	1.33–1.58 [†]	1.42	1.22–1.65 [†]
Atopic dermatitis	1.92	1.41–3.24 [‡]	1.35	1.16–1.58 [†]	1.49	1.06–2.10 [‡]
Asthma	1.82	0.93–3.54	1.11	0.90–1.38	1.10	0.66–1.82
Number of atopic diseases						
0	1.00	Reference	1.00	Reference	1.00	Reference
1	1.80	1.37–2.38 [†]	1.66	1.52–1.81 [†]	1.54	1.32–1.79 [†]
2	2.82	1.90–4.20 [†]	2.24	2.01–2.49 [†]	2.28	1.88–2.77 [†]
≥3	2.63	1.03–6.74 [‡]	2.85	2.33–3.50 [†]	2.75	1.78–4.23 [†]
P for trend	<.0001		<.0001		<.0001	

Adjusted for gender, urbanization.

* Adjusted for gender, urbanization, and mutual four allergic diseases.

[†] P < .001.

[‡] P < .01.

to sinusitis caused by streptococcal infections and caused various pediatric autoimmune neuropsychiatric disorders, including ADHD [18,25]. This may match a developmental pattern for a cluster of ADHD that begins in early childhood, and tends to become increasingly commonly beginning with school entry [7].

The causal results suggest that there are benefits from medication in management of ADHD. Although the stimulant drugs and tricyclic antidepressants are effective for ADHD, managing the associated atopic condition may facilitate improvement of symptoms and minimize medication for children with ADHD [11]. Therefore, the symptoms associated with AD and their medication could play major roles in the management of ADHD symptoms. AD and ADHD could be linked through the histamine pathway, suggesting that antihistamines may be effective for treating ADHD [18,25]. The potential therapeutic role for antihistamines in ADHD may offer a future alternative treatment choice for patients with dual diagnoses, but definite pathophysiologic mechanisms and clinical trials are required for further verification of treatment efficacy.

Limitations of this study include that information on clinical conditions, laboratory data, images, and severity of the disorders are not available. Moreover, residual confounding cannot completely be ruled out based on the available data. Neither the recording of the associated severity of comorbidities nor the educational background of the parents was available to enhance the possibilities to draw causal conclusions. These results cannot clarify whether treatment for a subclinical state or a state in a latent period, or whether these states influence the results.

Conclusions

Our results suggest that there are strong correlations between childhood ADHD and AD. If the association indeed proves to be causal, then effective treatment of atopic symptoms would have exciting potential as a strategy for the prevention of ADHD. We suggest that children with ADHD may require a combination of allergen prevention, and integrated diagnostic and management strategies. Moreover, determining and avoiding triggers for AD may reduce the predisposition to ADHD, and consequently reduce medical burden. We look forward the pathophysiologic research and longitudinal studies for follow-up of children with atopic conditions and neurobehavioral problem to add substantial evidence to support these correlations.

Acknowledgments

This study was supported by the National Sciences Council, Executive Yuan (grant numbers NSC 100-2621-M-039-001), Taiwan Department of Health Clinical Trial and Research Center for Excellence (grant number DOH102-TD-B-111-004) and Taiwan Department of Health Cancer Research Center of Excellence (DOH101-TD-C-111-005).

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