Prevalence of attention deficit/hyperactivity disorder in pediatric allergic rhinitis: A nationwide population-based study

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ABSTRACT

Allergic rhinitis (AR) is the most common chronic condition in pediatric populations. Characteristic symptoms in AR may bother daily activities and disturb sleep, leading to daytime inattention, irritability, and hyperactivity, which are also components of attention deficit/hyperactivity disorder (ADHD). Conflicting data exist in the literature regarding the relationship between ADHD and AR. The aim of this nationwide population-based study was to examine the prevalence and risk of ADHD among AR patients in a pediatric group. Data from a total of 226,550 pediatric patients <18 years old were collected from Taiwan's National Health Insurance Research Database from January 1 to December 31, 2005 and analyzed. We calculated the prevalence of allergic diseases based on various demographic variables, as well as in ADHD patients. We also used multivariable logistic regression to analyze the risk factors of ADHD. In 2005, the period prevalence rates of atopy and ADHD in patients <18 years of age were 15.35 and 0.6%, respectively. Pediatric patients with AR had a substantially increased rate of ADHD ($p < 0.001$) in terms of period prevalence and odds ratio. This significance existed across various demographic groups regardless of age, gender, area, or degree of urbanization. Neither comorbidity of atopic dermatitis nor bronchial asthma carried high risk for ADHD in AR patients. The present study revealed an increased rate of ADHD among AR patients. Therefore, evaluation of ADHD is advised for treatment of AR children.

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Allergic rhinitis (AR) is the most common chronic allergic disorder in pediatric populations. The very recent surveys (based on the International Study of Asthma and Allergies in Childhood questionnaire) conducted in Taipei and central Taiwan revealed its prevalence is as high as 30.9–44.9%.[1,2] Its characteristic symptoms include sneezing, rhinorrhea, pruritus, and nasal congestion.[3] Besides its physical complications, such as sinusitis, otitis media with effusion, snoring, and so on, sleep disturbances, poor school performance, and hyperactivity are all reported as mental complications.[4]

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Attention deficit/hyperactivity disorder (ADHD) is diagnosed by *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, criteria.[5] The estimated prevalence in children is 4–12%.[6] There are several common symptoms presented both in AR and in ADHD, such as sleep disturbances and cognitive dysfunction.[7,8] However, previous reports revealed conflicting data regarding the association between ADHD and AR.[9]

The National Health Insurance (NHI) system provides a comprehensive, unified, and universal health insurance program for almost all people in Taiwan. Approximately 98% of people in Taiwan participate in the NHI program.[10] Therefore, Taiwan's NHI Research Database (NHIRD) is one of the largest and most comprehensive nationwide population-based data sources currently available. In another study, we found AR, but not bronchial asthma (BA) or atopic dermatitis (AD) carried higher risk for ADHD in comparison with the general population.[11] The objective of this nationwide population-based study was to investigate the prevalence and risk of ADHD among children with AR.

MATERIALS AND METHODS

Database

The National Health Research Institutes provided a database of medical claims for 1,000,000 randomly selected persons, about 1/23 of the total population in

Taiwan, who are all under medical care from NHI. The data consisted of ambulatory care and inpatient care files, as well as registration records, including demographic data of the insured. There were no statistically significant differences in age, sex, and health care costs between the sample group and all enrollees.

Patients

We conducted this historic cohort study by collecting automated utilization data for all pediatric patients aged 0–17 years on January 1, 2005 and who were continuously enrolled in the NHI program between January 1 and December 31, 2005. Thus, 226,550 enrollees were included in this study.

The identified patients were divided into those with AR and a control group of general population. The AR consisted of all pediatric patients with at least one diagnosis of AR (code 477.xx in the International Classification of Diseases, Ninth Revision [ICD-9]) in an outpatient visit or hospitalization during 2005 (*i.e.*, provider-diagnosed AR). The diagnosis of AD and BA were based on at least one diagnosis fulfilled the ICD-9 code 691.xx and 493.xx. The diagnosis of ADHD was based on at least one hospital admission or at least two outpatient department visits with the main diagnosis of ADHD (code 314.xx in ICD-9). For protection of privacy, the identities of the patients, physicians, and institutions were scrambled in accordance with the Personal Electronic Data Protection Law.

Data Analysis

Pairwise comparisons were conducted to determine differences in demographic characteristics, including age, sex, region, and urbanicity, as well as the comorbidity of ADHD. We used chi-square test to compare differences in the prevalence rates of ADHD between patients with AR and general population according to age group, sex, region, and urbanicity. Finally, multivariable logistic regression was used to determine the factors affecting ADHD in patients with AR in 2005. SAS Version 9.2 (SAS Institute, Inc., Cary, NC) was used to analyze the data. In this study, the significance level was set at $p < 0.05$.

RESULTS

Of the 1,000,000 randomly selected people who were continuously enrolled in the NHI program in 2005, 226,550 (22.65%) were aged 0–17 years. The period prevalence of allergic disorders in the population was 15.4% ($n = 34{,}960$). The number of BA cases was 14,858 (6.2% of total enrollees), AR was 34,960 (15.3%), and AD was 10,620 (4.7%). Pairwise comparisons were performed to determine differences in demographic characteristics, including age, sex, region, and urbanicity, as shown in Table 1. Table 1 also shows the period prevalence of ADHD was 0.6% ($n = 1307$). AR patients had a higher prevalence of ADHD than general population (1.0% versus 0.5%; $p < 0.001$). The prevalence of AD and BA were also higher in AR patients (both, $p < 0.001$).

Table 2 shows the prevalence of ADHD in children. Compared with the general population, children with AR showed a higher prevalence in all age, sex, region, and urbanization groups. In AD group, those with AR revealed higher prevalence in ADHD (odds ratio [OR], 3.6; 95% CI, 2.14–5.15; $p < 0.001$). However, in the BA group, the prevalence of ADHD in those with AR and the general population were 1.1 and 0.8%, respectively (OR, 1.4; 95% CI, 0.99–2.02; $p = 0.057$).

Table 3 shows the factors associated with prevalence of ADHD in patients with AR, based on the results of logistic regression analysis. Compared with children <6 years old, children between 6 and 11 years had a higher risk for ADHD (OR, 2.06; 95% CI, 1.61–2.64). Boys showed a higher risk for ADHD (OR, 4.0; 95% CI, 2.98–5.36). Regarding region as a risk factor for ADHD, the only significant difference found was a lower risk in central Taiwan compared with eastern Taiwan (OR, 0.39; 95% CI, 0.18–0.83; $p = 0.015$); northern and southern Taiwan showed no differences in risk for ADHD compared with the eastern region. Urban area had a higher risk for ADHD than rural area (OR, 1.47; 95% CI, 1.11–1.94).

DISCUSSION

To the best of our knowledge, this is the first study using population-based NHI data to investigate the prevalence of ADHD in pediatric patients with AR. In another study,[11] we compared patients with AR, AD, or BA to the general population (nonatopy group) to investigate the risk for ADHD. We found AR, but not AD or BA, had a higher risk. So, in this study, we focused on AR to investigate its relationship to ADHD. Because the NHI program covers 98% of the Taiwanese population and 91% of medical institutions, the NHIRD offers unique and practical information for analyzing the relationship between AR and ADHD.

Our results revealed that the 1-year prevalence of ADHD in pediatric patients with AR was higher than that in the general population (1.0% versus 0.5%; $p < 0.001$). AR was associated with a higher prevalence of ADHD compared with the general population, regardless of age, sex, region, and urbanicity, as shown in Table 2. In the logistic regression model shown in Table 3, in those pediatric AR patients, aged between 6 and 11 years, male gender and living in urban region contributed to a higher risk for ADHD.

Regarding the comorbidity of atopy, in Table 1, our data did reveal higher prevalence of AD and BA in AR patients, as the consensus in multiple epidemiology

Table 1 **Demographic characteristics of persons with allergic rhinitis (AR) and the general population in 2005**

Variable	Total (n = 226,550)		General Population (n = 191,590)		with AR (n = 34,960)		p Value for χ^2-Test
	n	%	n	%	n	%	
Age (yr)							
<6	74,973	33.1	62,284	32.5	12,689	36.3	<0.001
6–11	81,529	36.0	67,484	35.2	14,045	40.2	
12–17	70,048	30.9	61,822	32.3	8226	23.5	
Gender							<0.001
Female	108,314	47.8	93,915	49.0	14,399	41.2	
Male	118,236	52.2	97,675	51.0	20,561	58.8	
Area in Taiwan							<0.001
North	111,616	49.3	93,151	48.6	18,465	52.8	
Middle	44,600	19.7	37,800	19.7	6800	19.5	
South	64,907	28.7	55,766	29.1	9141	26.2	
East	5427	2.4	4873	2.5	554	1.6	
Urbanization							<0.001
City	131,663	58.1	110,332	57.6	21,331	61.0	
Town	32,372	14.3	27,592	14.4	4780	13.7	
Rural area	62,515	27.6	53,666	28.0	8849	25.3	
ADHD							<0.001
No	225,243	99.4	190,640	99.5	34,603	99.0	
Yes	1307	0.6	950	0.5	357	1.0	
Atopic dermatitis							<0.001
No	215,930	95.3	183,837	96.0	32,093	91.8	
Yes	10,620	4.7	7753	4.0	2867	8.2	
Bronchial asthma							<0.001
No	211,692	93.4	185,325	96.7	26,367	75.4	
Yes	14,858	6.6	6265	3.3	8593	24.6	

ADHD = attention deficit/hyperactivity disorder.

studies in pediatric atopy.[11,12] Nevertheless, in Tables 2 and 3, the comorbidity of AR and BA did not show a higher risk for ADHD in patients with BA or AR alone.

In a systemic review published in 2010 about atopic diseases being a risk factor for ADHD, authors found 12 studies had a positive association between BA and ADHD.[13] However, in this review, authors commented on the inadequate methodology of many studies; so, they finally cited seven articles showed positive relationship between asthma and ADHD.[14–20] Among these seven studies, none ever investigated AR or comorbidity of AR as a risk factor at the same time. In our Table 1, we find 24.6% of AR patients had comorbidity of BA; and among 14,858 BA patients, 8593(57.8%) had AR. We suggest atopy comorbidity is an important factor in studying the relationship between atopy and ADHD.

In several earlier studies,[19,21–23] eczema was reported to be significantly associated with ADHD. However, AR was not reported in these studies except for one. Romanos *et al.* reported eczema (OR, 1.51; 95% CI, 1.24–1.84), but not AR (OR, 1.24; 95% CI, 0.99–1.56) or allergic comorbidity, was associated with ADHD.[21] In their study, the authors calculated the lifetime prevalence of atopic diseases for ADHD, but we only checked the period prevalence. Difference in methodology makes these two studies incomparable. As our database (NHIRD of Taiwan) started from 2000, we can not check lifetime prevalence at present. Atopic march was widely reported.[24,25] Previous reports showed the sequence of atopic manifestations: AD, followed by AR and asthma. One study reported 45% of infant AD patients had AR at 7 years of age.[26] Therefore, the AR patients in our study would have AD in their early childhood. Additional studies in this aspect are warranted.

From present knowledge, there was no known gene involving both atopic disease and ADHD. In a review published in 2010 about pathophysiology in AR,[27] it emphasized the local immunologic responses, including local IgE production, cytokines derived from epithelium, and H_4-histamine receptors. The mechanism

Table 2 **Prevalence of attention deficit/hyperactivity disorder in patients with and without allergic rhinitis (AR)**

Variable	General Population (n= 191,590)		with AR (n = 34,960)		OR	95% CI	p-Value for χ^2-Test
	n	%	n	%			
Age (yr)							
<6	245	0.4	97	0.8	2.0	15.4~2.47	<0.001
6–11	559	0.8	217	1.6	1.9	1.60~2.20	<0.001
12–17	146	0.2	43	0.5	2.2	1.58~3.12	<0.001
Gender							
Female	198	0.2	53	0.4	1.7	1.29~2.37	<0.001
Male	752	0.8	304	1.5	1.9	1.67~2.21	<0.001
Area							
North	575	0.6	235	1.3	2.1	1.78~2.41	<0.001
Middle	117	0.3	38	0.6	1.8	1.25~2.61	0.002
South	235	0.4	76	0.8	2.0	1.53~2.57	<0.001
East	23	0.5	8	1.4	3.1	1.38~6.94	0.011
Urbanization							
City	668	0.6	260	1.2	2.0	1.75~2.34	<0.001
Town	97	0.4	32	0.7	1.9	1.28~2.85	0.003
Rural area	185	0.3	65	0.7	2.1	1.61~2.84	<0.001
Comorbidity							
Atopic dermatitis							
No	924	0.5	323	1.0	2.0	1.77~2.29	<0.001
Yes	26	0.3	34	1.2	3.6	2.14~5.95	<0.001
Bronchial asthma							
No	903	0.5	266	1.0	2.1	1.81~2.39	<0.001
Yes	47	0.8	91	1.1	1.4	0.99~2.02	0.057

OR = odds ratio.

underlying the association between ADHD and AR is speculative at present. Some studies suggested that inflammatory cytokines released during atopic response may pass the blood–brain barrier[28] and activate neuroimmune mechanisms that involve behaviorally and emotionally relevant circuits.[29] There were some evidences in animal studies[30,31] and humans.[32] One human study showed the prefrontal cortex involvement by functional brain magnetic resonance, the structural and functional alterations in this area linked to ADHD symptoms.[33]

The possible explanations for the association between AR and ADHD in previous reports included shared symptoms, behavior complication from annoying AR symptoms, and associated sleep disturbances from AR, which led to daytime fatigue, inattention, and impulsivity.[4,9,34–36] In a 20-patient, double-blind, placebo-controlled study, Craig *et al.*[37] showed a decrease in sleep complaints and daytime somnolence in AR patients treated with nasal steroid. Romanos' report[21] further analyzed 6484 eczema patients, asking their parents if their children had sleep problems, and then only eczema patients with sleep problems had a higher risk for ADHD (OR, 2.67; 95% CI, 1.51–4.71). However, those eczema patients without sleep problems did not show higher risk (OR, 1.24; 95% CI, 0.83–1.84). However, the authors did not analyze the sleep problems in AR patients in this study. In terms of direct effect of treatment on patients with both AR and ADHD, there was a conference report in 2004 that showed combined therapy of cetirizine and stimulant for ADHD was superior to single-drug groups (cetirizine or stimulant alone) regarding both nasal and ADHD symptom scores.[38] At present, data are limited and additional studies regarding the therapeutic effect targeting both illnesses concurrently are needed.

Our study used a large health insurance database and assessed the data in 2005. The limitations of this study include no availability of some detailed information such as past atopic history, sleep problems, and quality of life. Replication of these results is needed to confirm the association between AR and ADHD.

In conclusion, the present study revealed an increased rate of ADHD among AR patients. As for

Table 3 **Multivariable logistic regression model of factors with prevalence of attention deficit/hyperactivity disorder in patients with allergic rhinitis**

Variable	OR	95% CI		*p* Value
		Lower	Upper	
Age (yr)				
<6	1.00	—	—	
6–11	2.06	1.61	2.64	<0.001
12–17	0.72	0.50	1.04	0.079
Gender				
Female	1.00	—	—	
Male	4.00	2.98	5.36	<0.001
Area				
East	1.00	—	—	
North	0.81	0.40	1.65	0.564
Middle	0.39	0.18	0.83	0.015
South	0.56	0.27	1.16	0.118
Urbanicity				
Rural	1.00	—	—	
Urban	1.47	1.11	1.94	<0.001
Suburban	0.92	0.60	1.40	0.687
Atopic dermatitis				
No	1.00	—	—	
Yes	1.25	0.87	1.80	0.226
Bronchial Asthma				
No	1.00	—	—	
Yes	0.95	0.75	1.22	0.711
$R^2 = 0.0605$				

OR = odds ratio.

clinical implications, allergists should be more aware of, detect, and treat, as well as educate our AR patients on the comorbidity of ADHD.

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Attention deficit/hyperactivity disorder (ADHD) is the most common childhood neurobehavioral disorder, with an estimated worldwide prevalence of at least 5% in school-age children.1 Impairing symptoms of ADHD persist in adulthood in as many as 65% of individuals with a childhood diagnosis.2. ADHD imposes an enormous burden on society in terms of psychological dysfunction, adverse vocational outcomes, stress on families, and societal financial costs. The US annual incremental costs of ADHD have been estimated at 143â€“266 billion USD.3.Â Despite being the most studied disorder in child psychiatry, the pathophysiology of ADHD remains elusive. Allergic rhinitis (AR) and other allergic diseases (AD), e.g., asthma, eczema and food allergy, is common in children. Characteristic symptoms of AR may result ...Â Characteristic symptoms of AR may result in daytime inattention, irritability and hyperactivity, which are also components of attention deficit hyperactivity disorder (ADHD). Conflicting data in previous studies exist regarding the relationship between ADHD and AD. The aim of this study was to examine the prevalence and risk of AR and self-reported allergic diseases in doctordiagnosed ADHD pediatric patients. We conducted a case-control study, where 78 patients and 103 non-ADHD controls were included. Previous studies have reported comorbidity of attention deficit and hyperactivity disorder (ADHD) and allergic diseases. The current study investigated ADHD like behavioral symptoms and parenting stress in pediatric allergic rhinitis. Methods. Eighty-seven children (6-13 years old) with allergic rhinitis and 73 age- and sex-matched children of control group were recruited. Diagnosis and severity assessments of allergic rhinitis were determined by a pediatric allergist.Â Routine evaluation and early management of ADHD symptoms in pediatric allergic rhinitis may benefit families of children with allergic rhinitis. Keywords: ADHD, Allergic rhinitis, Behavior problems, Children, Parenting stress. INTRODUCTION.