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ORIGINAL ARTICLE

Prevalence of attention-deficit/hyperactivity disorder in patients with pediatric allergic disorders: A nationwide, population-based study

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Background: Allergic disorders are common, chronic conditions in pediatric populations. The characteristic symptoms of allergic disorders mainly include bronchial asthma (BA), allergic rhinitis (AR), and atopic dermatitis (AD), all of which may 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 allergic disorders. The aim of this nationwide, population-based study is to examine the prevalence and risk of developing ADHD among allergic patients in a pediatric group.
Methods: Data from a total of 226,550 pediatric patients under 18 years of age were collected from Taiwan's National Health Insurance Research Database recorded from January 1 to December 31, 2005 and analyzed. We calculated the prevalence of allergic diseases based on various demographic variables, including ADHD. We also used multivariable logistic regression to analyze the risk factors of ADHD.
Results: In 2005, the period prevalence rates of allergic disorders and ADHD in persons under the age of 18 were 21.5% and 0.6%, respectively. Pediatric patients with allergic disorder(s) had a substantially increased rate of developing ADHD ($p < 0.001$) in terms of period prevalence and odds ratio (OR). This significance existed across various demographic groups regardless of age, gender, location, or degree of urbanization of their residence. BA and AR, but not AD, were

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determined to be risk factors for ADHD. Co-morbidities of allergic disorders, including AR+AD, AR+BA and AR+BA+AD, but not BA+AD, were also determined to increase the risk of ADHD.
Conclusion: Allergic disorders appear to increase the risk of ADHD in pediatric patients. Our detailed analysis shows that the main contributing factor is AR. Co-morbidity with AD, BA, and BA+AD in AR patients further increases the risk of ADHD.

Introduction

Allergic disorders are the most common chronic conditions in pediatric populations. The major disorders include bronchial asthma (BA), allergic rhinitis (AR), and atopic dermatitis (AD). Recent surveys (based on the questionnaire developed by the International Study of Asthma and Allergies in Childhood) have revealed that the prevalence rates of AR in Taipei and central Taiwan are as high as 43.6% and 44.4%, respectively. The rates of BA are 7.1% and 8.2% in these regions, respectively, and the rates of eczema are 4.1% and 8.8%, respectively.[1,2]

Attention-deficit/hyperactivity disorder (ADHD) is diagnosed according to the DSM-IV (Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition) criteria.[3] The estimated prevalence of ADHD in children is 4–12%.[4] There are several common symptoms that present both in allergic disorders and ADHD, such as sleep disturbance and cognitive dysfunction.[5–7] However, previous reports have revealed conflicting data regarding the association between ADHD and allergic disorders.[8]

The National Health Insurance (NHI) system provides a comprehensive, unified, and universal health insurance program for almost every person in Taiwan. Approximately 98% of the population of Taiwan participates in NHI.[9] Therefore, Taiwan's NHI Research Database (NHIRD) is one of the largest and most comprehensive nationwide population-based databases currently available. The objective of this nationwide, population-based study was to investigate the prevalence and risk of developing ADHD among children with allergic disorders.

Materials and methods

Database

NHIRD is maintained by the National Health Research Institutes. Our data set was comprised of medical claims for 1,000,000 persons who were randomly selected from NHIRD, which represents about 4.3% of the total population in Taiwan. All persons in the database are enrolled in the NHI system. The data consisted of ambulatory care and inpatient care files, including registration records and demographic data of the insured. There were no statistically significant differences in terms of age, sex, or healthcare costs between the sample group and all enrollees.

Patients

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

The identified patients were divided into two groups: the general population and those with common allergic disorders, including BA, AR, and AD. The allergic group consisted of all pediatric patients with at least one diagnosed case of BA, AR, or AD (codes 493.xx, 477.xx, and 691.xx in the International Classification of Diseases [ICD-9], 9th revision, respectively) who were listed as having an outpatient visit or hospitalization during 2005 (i.e., provider-diagnosed allergic disorder). The diagnosis of ADHD was based on at least one hospital admission or at least two out-patient department visits where the outcome was a diagnosis of ADHD (code 314.xx in ICD-9). In order to protect privacy, the identities of the patients, physicians, and institutions were scrambled in accordance with the personal electronic data protection regulations.[10]

Data analysis

Pairwise comparisons were conducted to determine differences in demographic characteristics, including age, sex, area, and urbanicity, as well as co-morbidity with ADHD. As previous NHIRD studies have shown,[11,12] we classified urbanicity into three groups: 1) the urban group implies those living in the "city" based on the address recorded in the database; 2) the suburban group includes those living in the "Jeng(鎮)" according to their address; and 3) those with addresses indicating "Xiang(鄉) were classified as living in a rural area. These geographical areas were defined using data from different branches of the NHI bureau in Taiwan, as performed in previous studies.[11,13] We used the χ^2test to compare differences in the prevalence rates of ADHD between patients with allergic disorders and those in the general population according to age, sex, location, and urbanicity. Finally, multivariable logistic regression was used to determine the factors that affected the presentation of ADHD in patients with an allergic disorder in 2005. SAS version 9.2 (SAS Institute, 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 NHI in 2005, 226,550 (22.65%) were 0–17 years of age. The period prevalence of allergic disorders in this population was 21.4% ($n = 48,457$). The number of BA cases was 14,858 (6.2% of total enrollees), the number of AR cases was 34,960 (15.3%), and the number of AD cases was 10,620 (4.7%). Pairwise comparisons of

patients with allergic disorders (n = 48,457) and the general population (n = 178,093) were performed in order to determine differences in demographic characteristics, including age, sex, location, and urbanicity, as shown in Table 1. Table 1 also shows that the period prevalence of ADHD was 0.6% (n = 1307). Allergic patients had a higher prevalence of ADHD than the general population (0.9% vs. 0.5%, $p < 0.001$).

Table 2 shows the prevalence of ADHD in children. Compared with the general population, children with allergic disorders showed a higher prevalence of ADHD regardless of age, sex, location, or urbanicity.

Table 3 shows the factors associated with the prevalence of ADHD in patients with allergic disorders, based on the results of the logistic regression analysis. Compared with children <6 years old, children between 6–11 years of age had a higher risk of developing ADHD (OR = 2.10; 95% CI = 1.85–2.39), and the 12–17-year-old group had a lower risk of developing ADHD (OR = 0.62; 95% CI = 0.51–0.74). Males also had a higher risk of developing ADHD (OR = 3.76; 95% CI = 3.26–4.32). Regarding location as a risk factor for ADHD, the only significant difference was a lower risk in central Taiwan compared with eastern Taiwan (OR = 0.61; 95% CI = 0.41–0.89); northern and southern Taiwan showed no difference in terms of the risk of developing ADHD compared with the eastern region. Patients in urban areas were at a higher risk of developing ADHD than patients in rural areas (OR = 1.58; 95% CI = 1.37–1.82).

In comparison with the general population, allergic patients showed an overall higher risk for developing ADHD (OR = 1.53; 95% CI = 1.38–1.75). When considering individual allergic disorders, AR and BA, but not AD, showed higher risks of being associated with ADHD (OR = 1.71, 95% CI = 1.48–1.98; OR = 1.38, 95% CI = 1.02–1.86; and OR = 0.73, 95% CI = 0.48–1.09, respectively). Comorbidities, including AR+BA, AR+AD, and AR+BA+AD, showed increased risks of association with ADHD (OR = 1.63, 95% CI = 1.26–2.06; OR = 2.14, 95% CI = 1.37–3.35; and OR = 2.02, 95% CI = 1.19–3.46, respectively). However, AD+BA was not shown to be a significant risk factor for the development of ADHD (OR = 0.72, 95% CI = 0.18–2.89).

Discussion

To the best of our knowledge, this is the first study to use population-based NHI data to investigate the prevalence of ADHD in pediatric patients with allergic disorders. Because the NHI program covers 98% of the Taiwanese population and 91% of medical institutions, the NHIRD offers unique and practical information that can be used to analyze the relationship between allergic disorders and ADHD.

Previous studies show conflicting results regarding the relationship between ADHD and allergic disorders in adolescents.[8] Two controlled studies reported increased ADHD symptoms according to clinical analyses of children with allergies.[14,15] However, negative findings were reported in other clinical allergy studies.[16,17] In a systemic review published in 2010 about allergic disorders as risk factors for the development of ADHD,[18] the authors found 12 studies that reported a positive association between BA and ADHD and six studies that reported a positive association between AD and ADHD. However, in this review, the authors commented that the methodologies of many of

Table 1 Demographic characteristics of patients with allergic disorders and general population

variable	Total (n = 226550)	General population (n = 178093)	with Allergic disease (n = 48457)	*p-value for χ^2test*
	n (%)	n (%)	n (%)	
Age(years old)				
<6	74973 (33.1)	53277 (29.9)	21696 (44.8)	<0.001
6-11	81529 (36.0)	64322 (36.1)	17207 (35.5)	
12-17	70048 (30.9)	60494 (34.0)	9554 (19.7)	
Gender				
Female	108314 (47.8)	87750 (49.3)	20564 (42.4)	<0.001
Male	118236 (52.2)	90343 (50.7)	27893 (57.6)	
Area				
North	111616 (49.3)	86101 (48.4)	25515 (52.7)	<0.001
Middle	44600 (19.7)	35316 (19.8)	9284 (19.2)	
South	64907 (28.7)	52081 (29.2)	12826 (26.5)	
East	5427 (2.4)	4595 (2.6)	832 (1.7)	
Urbanization				
Urban	131663 (58.1)	102507 (57.6)	29156 (60.2)	<0.001
Suburban	32372 (14.3)	25613 (14.4)	6759 (14.0)	
Rural	62515 (27.6)	49973 (28.0)	12542 (25.9)	
ADHD				
No	225243 (99.4)	177214 (99.5)	48029 (99.1)	<0.001
Yes	1307 (0.6)	879 (0.5)	428 (0.9)	

Table 2 Prevalence of ADHD in children with allergic disorders and the general population

variable	General population (n = 178093)	with Allergic disorders (n = 48457)	*Odds ratio*	*95% CI*	*p-value for χ^2test*
	n (%)	n (%)			
Age(years old)					
<6	219 (0.4)	123 (0.6)	1.38	1.11 ~ 1.72	0.005
6-11	519 (0.8)	257 (1.5)	1.86	1.60 ~ 2.17	<0.001
12-17	141 (0.2)	48 (0.5)	2.16	1.56 ~ 3.00	<0.001
Gender					
Female	182 (0.2)	69 (0.4)	1.62	1.23 ~ 2.14	<0.001
Male	697 (0.8)	359 (1.3)	1.68	1.48 ~ 1.91	<0.001
Area					
North	532 (0.6)	278 (1.1)	1.77	1.53 ~ 2.05	<0.001
Middle	105 (0.3)	50 (0.5)	1.82	1.30 ~ 2.54	<0.001
South	220 (0.4)	91 (0.7)	1.68	1.32 ~ 2.15	<0.001
East	22 (0.5)	9 (1.1)	2.27	1.04 ~ 4.95	0.044
Urbanization					
Urban	619 (0.6)	309 (1.1)	1.76	1.54 ~ 2.02	<0.001
Suburban	87 (0.3)	42 (0.6)	1.83	1.27 ~ 2.65	0.002
Rural	173 (0.4)	77 (0.6)	1.78	1.36 ~ 2.33	<0.001

Table 3 Logistic regression model of factors with prevalence of ADHD in pediatric allergic patients

variable	Odds ratio	95% CI		*p-value*
		Lower	Upper	
Age(years old)				
<6	1.00	—	—	
6-11	2.10	1.85	2.39	<0.001
12-17	0.62	0.51	0.74	<0.001
Gender				
Female	1.00	—	—	
Male	3.76	3.28	4.32	<0.001
Area				
East	1.00	—	—	
North	1.12	0.78	1.61	0.528
Middle	0.61	0.41	0.89	0.011
South	0.81	0.56	1.17	0.265
Urbanization				
Rural	1.00	—	—	
Urban	1.58	1.37	1.82	<0.001
Suburban	0.99	0.80	1.23	0.930
Allergic condition				
no allergic disorders	1.00	—	—	
AR or BA or AD	1.56	1.38	1.75	<0.001
AR	1.71	1.48	1.98	<0.001
AD	0.73	0.48	1.09	0.124
BA	1.38	1.02	1.86	0.039
AR and AD	2.14	1.37	3.35	0.001
AR and BA	1.63	1.28	2.06	<0.001
AD and BA	0.72	0.18	2.89	0.639
AR and BA and AD	2.02	1.19	3.46	0.010

R-Square = 0.0666.

these studies were inadequate, so they finally cited seven articles about asthma[19–25] and four articles about AD[26–29] that showed a positive relationship with ADHD. In our study, we found that AD alone does not have positive association with ADHD. AD+AR had a higher OR than AR alone. However, AD+BA did not demonstrate a positive association with ADHD. Among published reports, however, none investigated co-morbidities as possible risk factors at the same time. In this systemic review, there were only two previous studies available that used the ICD system for the diagnosis of ADHD and allergic disorders. The study by Secnik et al reports a positive association between asthma and ADHD,[22] and the study by Schmitt et al reports a positive association between AD and ADHD.[26] Neither study mentions co-morbidity with asthma or AD.

Investigations examining allergic disorders in children with ADHD also report conflicting results. Blank et al reported increased rates of allergies among children with ADHD.[30] In contrast, another control-matched study revealed no difference in the rates of allergies between children with ADHD and controls.[31] A large community study followed 1037 children from the ages of 3–18 years, but no associations between ADHD and allergic disorders were found, either clinically or biologically.[32] A recent study by Brawley et al examined the prevalence of AR in 30 children with ADHD. Among these children, 80% showed AR symptoms, 61% were positive for the skin prick test, and 100% had a family history of allergies.[33]

Analysis of the large database used in this study revealed associations between some allergies and ADHD. We analyzed associations between BA, AR, AD, and combinations of these conditions with ADHD. AR was found to be the most important contributing factor for the development of ADHD among the various allergies that were investigated. AR carried a higher risk for the development of ADHD than BA or AD. Co-morbid conditions with AR all showed a higher risk for the development of ADHD. In our study, AD was not

identified as a risk factor for the development of ADHD. BA demonstrated an increased risk, but when combined with AD there was no increased risk of developing ADHD. Previously reported conflicting findings may be attributable to the inclusion of all allergic disorders into a single group due to the small size of the study population, which would therefore prohibit more specific groupings of allergic conditions. We were able to utilize a large research database, so it was possible to analyze all combinations of allergic disorders, as shown in Table 3. In previous reports, co-morbid conditions were not analyzed.

Possible explanations for the association between AR and ADHD in previous reports include shared symptoms, behavioral complications related to annoying AR symptoms, and AR-associated sleep disturbance that can lead to daytime fatigue, inattention, and impulsivity.[7,8,34] In the largest cohort study ever conducted in Germany, AD was associated with ADHD.[26] However, the same researchers further investigated sleep disturbance as a possible confounding factor in this cohort. They found that only those AD patients with sleep disturbance were at a higher risk of developing ADHD.[27] Craig et al demonstrated that intranasal steroids decrease nasal symptoms, sleep complaints, and daytime somnolence.[35] Regarding the direct effects of treatment on patients with both AR and ADHD, a conference report published in 2004 described a combination therapy of cetirizine and a stimulant for treating ADHD that was superior to single-drug therapies (cetirizine or the stimulant alone), in terms of both nasal and ADHD symptoms scores.[36]

NHIRD only provides data on treatment prevalence rates related to allergies and ADHD. The prevalence rates were inevitably lower than those obtained by questionnaire or physician surveys.[1,2,4] We could not analyze each patient's allergy sensitization status, sleep condition, or family history. Nevertheless, NHIRD covers almost the entire population in Taiwan, so these data may be of value for researchers and clinicians.

In conclusion, this study shows associations between allergic disorders, especially AR, and ADHD. Further analysis of the AR groups, including an epidemiological study and an investigation into the therapies that concurrently target both disorders are needed. We recommend that pediatricians, especially those with expertise in allergies, be aware of the potential for ADHD in their allergic patients. The clinical history of ADHD should be considered when providing treatment. Better health education is also needed. Our data provide evidence that may be used to educate caregivers and increase awareness about symptoms related to allergies and ADHD.

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