

Association of pediatric allergic rhinitis with the ratings of attention-deficit/hyperactivity disorder

Bohai Feng, M.D., Haiyong Jin, M.D., Haijie Xiang, M.D., Bangliang Li, M.D., Xiuxiu Zheng, M.D., Ruru Chen, M.D., Yunbin Shi, M.D., Si Chen, M.D., and Bobei Chen, M.D.

ABSTRACT

Background: Allergic rhinitis (AR) is currently the most prevalent allergic disease in children and adolescents.

Objective: Surveys conducted by population-based studies of East Asia revealed an increased prevalence of behavioral disorders in patients with AR. Thus, in this study, we explored the prevalence of attention-deficit/hyperactivity disorder (ADHD) in pediatric patients with AR.

Methods: A total of 333 children (6–12 years of age) with AR and a total of 322 age-matched controls were included in this study. An otorhinolaryngologist diagnosed all AR cases and evaluated the severity of the disease. Skin-prick test results for 18 major allergens, Paediatric Rhinoconjunctivitis Quality of Life Questionnaire (PRQLQ), Child Behavior Checklist (CBCL), and Swanson, Nolan, and Pelham version IV (SNAP-IV) scores were recorded.

Results: In total, 320 age-matched controls and 323 children with AR completed the study. With respect to the Total Nasal Symptom Score and the PRQLQ, the condition of the experimental group was more serious than that of the controls. The scores on the hyperactivity/impulsivity and inattention subscales, which evaluate ADHD symptoms, and those on the CBCL subscales were significantly higher in patients with AR than in the controls (all *p* values were <0.01). From the results of the Pearson correlation, we deduced that there were significant positive correlations between the AR-related data and each subscale of the CBCL and SNAP-IV in the AR group. Moreover, two basic characteristics (males and environmental exposure to tobacco smoke) present significant positive and age showed a significant negative correlations affect ADHD symptom in both the AR group and the control group. Also, in the “pure AR” group, hierarchical regression analyses were performed to determine the subtests of the PRQLQ, which are significant predictors of SNAP-IV and CBCL.

Conclusions: Apart from AR per se, the possible comorbidities of impulsivity and inattention are important when managing children with AR. It is essential to evaluate the symptoms of ADHD in children and adolescents with AR.

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In recent years, allergic rhinitis (AR) has affected 1.4 billion individuals,¹ i.e., ~10 to 30% of adults and at least 40% of children,^{2–4} and is still on the rise. Poorly controlled AR may affect work efficiency, sleep quality, and quality of life.^{5,6} Several large-scale studies^{4,7,8} confirmed that AR, which can lead to various discomforts (i.e., fatigue, cognitive dysfunction, and depression),^{6,9} is prevalent worldwide and mostly remains undiagnosed. In the United States, the total annual direct medical expenditure on AR was ~\$3.4 billion, of which almost half was spent on prescription medications.¹⁰ Nevertheless, many patients with AR do not follow standard therapies. A survey conducted in America showed that the burden of AR in children has been significantly underestimated.^{2,3} In the recent decade, there has been a marked increase in the prevalence of AR in China, and it has become an unignorable health concern for patients with AR, especially children. A number of cross-sectional surveys revealed the prevalence of AR in numerous major cities.¹¹

However, many authoritative surveys^{12–15} revealed an increased level of behavioral disorders in children with allergic disorders, especially with AR. Attention-deficit/hyperactivity disorder (ADHD) is the most widely occurring behavioral disorder in school-age children. ADHD affects ~5.29% of school-age children and adolescents,¹⁶ and has a prevalence of 2 to 16% in the United States¹⁷ and 1.3 to 13.6% in China.¹⁸ ADHD affects several functional areas, especially the social domain,¹⁹ and imposes great economic burdens on affected families and society.^{20,21} An ADHD diagnosis is dependent on clinical observations, rating scales from multiple informants (e.g., teachers, parents), and documentation of clinically significant impairment.²² Hy-

peractivity, inattention, and impulsive behavior are the principal symptoms of ADHD.²³ Moreover, ADHD, especially in children, often presents with complications, including externalizing and internalizing behaviors.²⁴

The relationship between atopic disease and ADHD has been investigated for >10 years, and the findings remain controversial.^{15,25–27} It is interesting to note that poorly controlled AR disturbs sleep patterns and daily activities, which may lead to daytime inattention, irritability, and hyperactivity. These behavioral symptoms are mostly seen in children with ADHD.²⁸ The prevalence of ADHD and allergic disease has simultaneously increased worldwide,²⁹ and the age range of patients with AR is similar to that of patients with ADHD.^{30,31} Two studies^{32,33} indicated that some children with AR exhibit ADHD. Recently, Yang *et al.*³⁴ recommended that children with AR and borderline ADHD symptoms who do not completely meet the ADHD diagnostic criteria should initially be treated and then monitored for any improvement in ADHD symptoms. However, inattention and hyperactivity in children with AR have not been objectively measured. To our knowledge, no previous work revealed the association between AR and ADHD by using objective and well-validated measures in Chinese children and adolescents. Therefore, in this study, we explored the attention and impulsivity of children with AR compared with those of the controls and identified the factors that influence these behaviors.

METHODS

Study Participants

Children ages 6–12 years were recruited from August 2015 to June 2016 at the ear, nose, and throat outpatient clinic of the Second Affiliated Hospital of Wenzhou Medical University. The study was approved by the institutional review board of the Second Affiliated Hospital of Wenzhou Medical University. All the parents and/or participants (if able to understand the purpose of the study) signed informed consent forms before the assessment. Children with AR were enrolled in accordance with the 2008 Allergic Rhinitis and its Impact on Asthma guidelines.³⁵ We administered the questionnaires,

From the Department of Otolaryngology, The Second Affiliated Hospital and Yuying Children's Hospital of Wenzhou Medical University, Wenzhou, Zhejiang, China
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Address correspondence to Bobei Chen, M.D., Department of Otolaryngology, The Second Affiliated Hospital and Yuying Children's Hospital of Wenzhou Medical University, College West Road no. 109, Wenzhou, Zhejiang, 325027, China
E-mail address: wzbobei@hotmail.com

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Table 1 Subject characteristics and AR scores

	AR (n = 323)	Control (n = 320)	Statistics	p
Age, mean $\pm$ SD, y	9.25 $\pm$ 1.85	8.94 $\pm$ 1.96	1.098*	0.273
Boys/girls, no.	173/150	161/159	0.679#§	0.410
Environmental tobacco smoking, no./total no. (%)	120/203 (37.2)	112/208 (35)	0.323#¶	0.570
TNSS, mean $\pm$ SD	5.60 $\pm$ 2.08	1.44 $\pm$ 0.60	15.440*	<0.001
PRQLQ score, mean $\pm$ SD				
Nose symptoms	2.61 $\pm$ 1.30	1.38 $\pm$ 0.42	7.412*	<0.001
Eye symptoms	1.58 $\pm$ 0.62	1.14 $\pm$ 0.19	4.951*	0.009
Practical problems	2.11 $\pm$ 1.13	1.21 $\pm$ 0.40	4.382*	<0.001
Other symptoms	1.49 $\pm$ 0.61	1.12 $\pm$ 0.19	5.826*	<0.001
Activity limitations	1.39 $\pm$ 0.75	0.99 $\pm$ 0.28	6.460*	0.007
Overall	1.85 $\pm$ 0.68	1.12 $\pm$ 0.35	5.423*	<0.001

AR = Allergic rhinitis; SD = standard deviation; TNSS = Total Rhinitis Symptoms Score; PRQLQ = Paediatric Rhinoconjunctivitis Quality of Life Questionnaire.

*Independent samples t-test.

χ^2 test.

§Cramer's ϕ = 0.032.

¶Cramer's ϕ = 0.022.

recorded basic demographic information, and performed skin-prick tests for 18 major allergens. Any child with negative test results to inhalant allergy testing was excluded. Because antihistamines and corticosteroids influence cognition and performance³⁶ in children with AR, we enrolled only those children who had not taken any such medications in the past 6 months. Age-matched children without AR or ADHD who visited our child health clinic served as controls in the same period. The skin-prick test for 18 major allergens was performed on the control group, and any child with positive test results was excluded. The controls were age and frequency matched to the AR group according to age category (6–7, 8–9, 10–12 years). Any child who exhibited mental retardation, developmental delay, or epilepsy was excluded.

AR Symptom Scores

The Total Rhinitis Symptoms Score (TNSS), the most common outcome reported in the literature, is the sum of the scores of the four nasal symptoms (watery rhinorrhea, sneezing, nasal obstruction, and nasal pruritus) on a scale of 0 to 3 (0, none; 1, mild; 2, moderate; and 3, severe).

Skin-Prick Tests

Skin-prick tests were performed by using 18 common Chinese inhaled and food allergens and negative and positive controls (ALK-Abelló, Hørsholm, Denmark). The allergens tested were those of *Dermatophagoides pteronyssinus*, *Dermatophagoides farinae*, cockroach, the molds *Alternaria alternata* and *Aspergillus fumigatus*, baker's yeast, wheat, sieversiana pollen, sesame, croaker, crab, silk, shrimp, cat, dog, egg, milk, soybean, and peanut. A mean wheal diameter of ≥ 3 mm that of the negative control was considered positive. Atopy was considered to be present when one or more allergens yielded a positive skin-prick test result.

Paediatric Rhinoconjunctivitis Quality of Life Questionnaire

The Paediatric Rhinoconjunctivitis Quality of Life Questionnaire (PRQLQ, Hoechst Marion Roussel Inc., Kansas City, MO)³⁷ consists of 23 questions, which cover five aspects: nose symptoms, eye symptoms, practical problems, other symptoms, and activity limitations. The score of each question ranges from 0 to 6. A score of 0 indicates no impairment, whereas a score of 6 implies maximum impairment. The children were asked to score their past 7 days of experiences. To guarantee the accuracy of the experiment, the questionnaire was

Table 2 The frequency of the ages of the children who participated in the study

Age Category	Age, y	AR Group, no. (%) (n = 323)	Control Group, no. (%) (n = 320)
6–7 y	6	24 (7.4)	53 (16.6)
	7	41 (12.7)	11 (3.4)
8–9 y	8	57 (17.6)	95 (29.7)
	9	58 (18.0)	20 (6.3)
10–12 y	10	38 (11.8)	69 (21.6)
	11	60 (18.6)	22 (6.9)
	12	45 (13.9)	49 (15.3)

AR = Allergic rhinitis.

administered by a trained interviewer (X.Z.). In addition, the parents were not allowed to be with the child during the interview. Validation of the standardized version of the PRQLQ showed it to have satisfactory levels of reliability and concurrent validity.³⁸

Child Behavior Checklist

The Child Behavior Checklist (CBCL, University of Vermont, Research Center for Children, Burlington, VT),³⁹ which consists of 119 items that explore behavioral problems in the child over the past 6 months, is widely used to assess both the problems and social adaptation. It contains 12 subscales that evaluate anxiety/depression, somatic complaints, withdrawal, thought problems, attentional problems, delinquent behavior, aggressive behavior, emotional instability, internalizing symptoms, externalizing symptoms, and social problems. The parents respond by using a three-point scale. The Chinese version of the CBCL was used to yield reliable and valid results.⁴⁰

The Swanson, Nolan, and Pelham Version IV Scale

The Swanson, Nolan, and Pelham version IV scale (SNAP-IV) is a 26-item scale used to evaluate ADHD symptoms and its severity.⁴¹ It includes 18 questions on ADHD symptoms (9 on inattention and 9 on hyperactivity/impulsivity) and 8 questions on oppositional defiant disorder symptoms. Each item is scored on a scale of 0 (not at all) to 3 (very much). The Chinese version of the SNAP-IV has been used to yield reliable and valid results.⁴²

Table 3 Comparison of CBCL and SNAP-IV between the AR group and the control group

	Groups	No.	Mean $\pm$ SD	η^2	F Statistics*	p
AR and control						
CBCL						
Attentional problems	AR	323	2.56 $\pm$ 1.569	0.2118	172.262	<0.001
	Control	320	1.31 $\pm$ 0.667			
Emotional instability	AR	323	4.54 $\pm$ 3.142	0.1124	81.143	<0.001
	Control	320	2.86 $\pm$ 1.127			
Internalizing problem	AR	323	4.64 $\pm$ 2.210	0.0088	43.531	<0.001
	Control	320	3.50 $\pm$ 2.171			
Social problem	AR	323	10.51 $\pm$ 1.597	0.1119	80.765	<0.001
	Control	320	11.62 $\pm$ 1.534			
SNAP-IV						
Inattention	AR	323	9.38 $\pm$ 5.812	0.0572	38.909	<0.001
	Control	320	7.09 $\pm$ 3.072			
Hyperactivity/impulsivity	AR	323	8.13 $\pm$ 5.338	0.1900	150.331	<0.001
	Control	320	3.86 $\pm$ 3.227			
Pure AR and control						
CBCL						
Attentional problems	Pure AR	248	2.64 $\pm$ 1.008	0.3861	356.045	<0.001
	Control	320	1.31 $\pm$ 0.667			
Emotional instability	Pure AR	248	4.38 $\pm$ 1.923	0.1967	138.566	<0.001
	Control	320	2.86 $\pm$ 1.127			
Internalizing problem	Pure AR	248	4.58 $\pm$ 2.315	0.0545	32.625	<0.001
	Control	320	3.50 $\pm$ 2.171			
Social problem	Pure AR	248	9.92 $\pm$ 1.342	0.2525	191.170	<0.001
	Control	320	11.62 $\pm$ 1.534			
SNAP-IV						
Inattention	Pure AR	248	9.79 $\pm$ 4.672	0.1081	68.615	<0.001
	Control	320	7.09 $\pm$ 3.072			
Hyperactivity/impulsivity	Pure AR	248	7.92 $\pm$ 4.113	0.2349	173.796	<0.001
	Control	320	3.86 $\pm$ 3.227			

CBCL = Child Behavior Checklist, SNAP-IV = Swanson, Nolan, and Pelham, version IV Rating Scale; AR = allergic rhinitis, SD = standard deviation.

*Multivariate analysis of covariance (with age and sex as covariates).

Statistical Analysis

SPSS version 19.0 (StataCorp LP, College Station, TX) was used for statistical analysis. The independent samples *t*-test was used to compare differences in age, TNSS, and the PRQLQ score between the AR group and the control group. The χ^2 test was used to compare sex differences and environmental exposure to tobacco smoke between the groups. According to other related literature,^{43–45} we added the “pure AR” group in our study to specifically explore the relationship between AR and ADHD symptoms. The pure AR group is a subset of the original AR group that excluded multiple atopic diseases (allergic asthma, atopic dermatitis, food allergy). The multivariate analysis of covariance test was used to examine the differences in subscales of the CBCL and SNAP-IV according to the two parts (AR and controls, and pure AR and controls) while controlling for age and sex. By using the mean $\pm$ standard deviation of controls, we obtained the effect size^{46,47} estimates for each group. This value showed the difference in standard deviation units between the observed scores of the AR group and the pure AR group. The interpretation obtained from η^2 ⁴⁶ is used to indicate the effect degree. In detail, $0.01 \leq \eta^2 < 0.06$ shows a small effect, whereas $\eta^2 \leq 0.14$ means a large effect and $0.06 \leq \eta^2 < 0.14$ indicates a medium effect.

The relationship between possible explanatory parameters (age, male sex, TNSS, duration of rhinitis in years, other atopic diseases, environmental exposure to tobacco smoke, number of positive allergens, and PRQLQ) and the subscales of CBCL and SNAP-IV were evaluated by the Pearson correlation in the AR and pure AR groups. A similar measure was used to assess the relationship between basic

characteristics (age, male sex, environmental exposure to tobacco smoke) and the subscales of CBCL and SNAP-IV in the non-AR group. Also, in pure AR group, hierarchical (four-stage) regression analyses were performed to determine if subtests of the PRQLQ are significant predictors of SNAP-IV and CBCL. Controls for demographic and social background, sex (female, 0; male, 1), age, and environmental tobacco smoking (exposure, 1; no exposure, 0) were entered in the first step of each regression, followed by the number of positive allergens (step 2), duration of rhinitis in years (step 3), and subtests of the PRQLQ (step 4). The number of positive allergens, duration of rhinitis in years, and subtests of PRQLQ were centered before the calculation of the interaction terms. The following coefficients are displayed in the Results section: (i) the square of the multiple correlation coefficient (R^2) for the whole model after the final step, (ii) stepwise changes in R^2 (ΔR^2), and (iii) each predictor variable (for the final model). Significant effects of interaction are plotted to interpret the direction of the relationships. All the tests were two-tailed, and a $p < 0.05$ was considered to reflect statistical significance.⁴⁸

RESULTS

Participants and AR Symptom Scores

In total, 643 children (323 in the AR group and 320 in the control group) completed the study. Nine children (seven in the AR group and two in the control group) were excluded because of noncompli-

Table 4 The correlations between the possible explanatory parameters and each subscale of the CBCL and SNAP-IV in the AR group

	CBCL, <i>r</i>				SNAP-IV, <i>r</i>	
	Attentional Problems	Emotional Instability	Internalizing Problem	Social Problem	Inattention	Hyperactivity/Impulsivity
PRQLQ						
Nose symptoms	0.48*	0.47*	0.34*	-0.38*	0.54*	0.38*
Eye symptoms	0.39*	0.32*	0.41*	-0.37*	0.43*	0.36*
Practical problems	0.50*	0.52*	0.42*	-0.43*	0.55*	0.42*
Other symptoms	0.62*	0.54*	0.39*	-0.40*	0.63*	0.49*
Activity limitations	0.52*	0.46*	0.33*	-0.31*	0.48*	0.47*
Age	-0.59*	-0.47*	-0.52*	0.49*	-0.64*	-0.52*
Male sex	0.63*	0.49*	0.51*	-0.39*	0.61*	0.48*
TNSS	0.45*	0.39*	0.32*	-0.36*	0.59*	0.40*
Multiple AD	0.42*	0.45*	0.39	-0.42*	0.54*	0.46*
Duration of AR	0.60*	0.43	0.36*	-0.56*	0.63*	0.47
Positive allergens	0.46*	0.38*	0.40*	-0.45*	0.49*	0.49*
Environmental tobacco smoking	0.45*	0.36	0.42*	-0.50*	0.48*	0.51

CBCL = Child Behavior Checklist; SNAP-IV = Swanson, Nolan, and Pelham, version IV rating scale; AR = allergic rhinitis; PRQLQ: Paediatric Rhinoconjunctivitis Quality of Life Questionnaire; TNSS = Total Rhinitis Symptoms Score; AD = atopic disease.

* $p < 0.05$.

Table 5 The correlations between the possible explanatory parameters and each subscale of the CBCL and SNAP-IV in the pure AR group

	CBCL, <i>r</i>				SNAP-IV, <i>r</i>	
	Attentional Problems	Emotional Instability	Internalizing Problem	Social Problem	Inattention	Hyperactivity/Impulsivity
PRQLQ						
Nose symptoms	0.46*	0.45*	0.36*	-0.40*	0.52*	0.41*
Eye symptoms	0.41*	0.34*	0.40*	-0.39*	0.41*	0.38*
Practical problems	0.49*	0.51*	0.43*	-0.41*	0.52*	0.41*
Other symptoms	0.59*	0.52*	0.41*	-0.41*	0.61*	0.50*
Activity limitations	0.53*	0.45*	0.35*	-0.33*	0.49*	0.46*
Age	-0.57*	-0.48*	-0.50*	0.51*	-0.62*	-0.54*
Male sex	0.65*	0.51*	0.49*	-0.38*	0.59*	0.47*
TNSS	0.43*	0.37*	0.31*	-0.39*	0.61*	0.41*
Duration of AR	0.39*	0.38	0.41*	-0.54*	0.41*	0.42
Positive allergens	0.47*	0.36*	0.41*	-0.42*	0.48*	0.47*
Environmental tobacco smoking	0.43*	0.38*	0.41*	-0.49*	0.46*	0.49*

CBCL = Child Behavior Checklist; SNAP-IV = Swanson, Nolan, and Pelham, version IV Rating Scale; AR = allergic rhinitis; PRQLQ = Paediatric Rhinoconjunctivitis Quality of Life Questionnaire; TNSS = Total Nasal Symptom Score.

* $p < 0.05$.

ance, and three children with AR were excluded because they had not returned the questionnaires. We found no difference between the two groups based on exposure to environmental tobacco smoke, age, or sex distribution. The AR symptom score (TNSS) was significantly higher in the AR group (Table 1). The frequency of children in each age category is illustrated in Table 2. Also, 248 children (138 boys and 110 girls), ages 6 to 12 years, with only AR were selected in the pure AR group, *i.e.*, children with multiple atopic diseases (allergic asthma, atopic dermatitis, and food allergy) were excluded from the original AR group.

PRQLQ

The overall score of experiments was noticeably higher than that of the controls. The two groups showed a marked difference with regard to the five aspects investigated, which were nose symptoms, eye symptoms, practical problems, other symptoms, and activity limitations (Table 1).

CBCL

Emotional and behavioral problems were more evident in children with AR than in the controls, and the AR group scored higher on the following three subscales: attentional problems ($\eta^2 = 0.2118$, $F = 172.262$, $p < 0.001$), emotional instability ($\eta^2 = 0.1124$, $F = 81.143$, $p < 0.001$), and internalizing problems ($\eta^2 = 0.0088$, $F = 43.531$, $p < 0.001$). Children with AR had lower social competence scores than controls ($\eta^2 = 0.1119$, $F = 80.765$, $p < 0.001$) (Table 3).

SNAP-IV Scores

The SNAP-IV scores (calculated by using questionnaires completed by the parents) of the control and AR groups differed significantly. Compared with the controls, children with AR had significantly higher inattention and hyperactivity/impulsivity subscale scores: $\eta^2 = 0.0572$, $F = 38.909$, $p < 0.001$; and $\eta^2 = 0.1900$, $F = 150.331$, $p < 0.001$, respectively (Table 3).

Table 6 The correlations between the possible explanatory parameters and each subscale of the CBCL and SNAP-IV in the control group

	CBCL, <i>r</i>				SNAP-IV, <i>r</i>	
	Attentional Problems	Emotional Instability	Internalizing Problem	Social Problem	Inattention	Hyperactivity/Impulsivity
Age	−0.56*	−0.48*	−0.51*	0.45*	−0.59*	−0.53*
Male sex	0.59*	0.51*	0.49*	−0.37*	0.58*	0.46*
Environmental tobacco smoking	0.46*	0.35*	0.40	−0.52*	0.47*	0.49*

CBCL = Child Behavior Checklist, SNAP-IV = Swanson, Nolan, and Pelham, version IV Rating Scale.

**p* < 0.05.

Table 7 Hierarchical linear regression in the pure AR group

	CBCL								SNAP-IV			
	Attentional Problems		Emotional Instability		Internalizing Problem		Social Problem		Inattention		Hyperactivity/Impulsivity	
	ΔR^2	β	ΔR^2	β	ΔR^2	β	ΔR^2	β	ΔR^2	β	ΔR^2	β
Step 1: Covariates	0.076*		0.063*		0.034*		0.041*		0.081*		0.079*	
Age		−0.065*		−0.122*		−0.127*		0.273*		−0.424*		−0.581*
Male sex		0.045*		0.199*		0.228*		−0.271*		1.284*		1.398*
Environmental tobacco smoking		0.398*		0.123*		0.167		−0.092		0.546*		1.057*
Step 2	0.000		0.008		0.003		0.002		0.001		0.014*	
Positive allergens		0.034		0.095		0.034		−0.015		0.479*		0.235
Step 3	0.002		0.001		0.000		0.003		0.002		0.005	
Duration of AR		0.028		0.118		0.061		−0.029		−0.084		0.105
Step 4: PRQLQ	0.136*		0.124*		0.070*		0.087*		0.155*		0.169*	
Nose symptoms		0.246*		0.187*		0.245*		−0.213*		0.742*		1.123*
Eye symptoms		0.148*		0.201*		0.237*		−0.169*		0.323*		0.498*
Practical problems		0.076*		0.081*		0.141		−0.079		0.176*		0.568*
Other symptoms		0.089*		0.155		0.089*		−0.134*		1.137*		0.983*
Activity limitations		0.124*		0.236*		0.204*		−0.179*		0.342*		0.347*
Total ΔR^2	0.215*		0.196*		0.108*		0.133*		0.239*		0.267*	

AR = Allergic rhinitis; CBCL = Child Behavior Checklist, SNAP-IV = Swanson, Nolan, and Pelham, version IV Rating Scale; PRQLQ = Paediatric Rhinoconjunctivitis Quality of Life Questionnaire.

**p* < 0.05.

Interitem Correlations between Instruments of Measure

Presented in Tables 4 and 5, it can be clearly seen that possible explanatory parameters (age, male sex, TNSS, duration of rhinitis in years, other atopic diseases, environmental exposure to tobacco smoke, the number of positive allergens, and PRQLQ scores) and each subscale of the CBCL and SNAP-IV were positively related in the AR and pure AR groups. Moreover, we concluded that the basic characteristics (age, male, environmental exposure to tobacco smoke) were closely related to the subscale of CBCL and SNAP-IV in the non-AR group of children (Table 6). With regard to the question of whether subtests of the PRQLQ are significant predictors in the pure AR group of the SNAP-IV and CBCL, as shown in Table 7, after controlling for sex, age, and environmental tobacco smoking, the number of positive allergens explained the significant amount of variance only seen in the hyperactivity/impulsivity subscale score (which explained the 1.9% of variance in step 2). However, the duration of rhinitis in years proved to be a nonsignificant predictor of the SNAP-IV and CBCL (step 3). Also, the subtests of the PRQLQ were significant predictors of the SNAP-IV and CBCL (step 4).

DISCUSSION

We found that children with AR had higher SNAP-IV symptom scores and also scored higher on the ADHD-related behavioral prob-

lem CBCL subscale than did the children in the control group. AR symptoms are suggested to directly cause cognitive distraction and inattention. We also examined how AR-related data (TNSS, duration of rhinitis in years, other atopic diseases, the number of positive allergens, and PRQLQ) and basic characteristics (age, male sex, environmental exposure to tobacco smoke) affected ADHD symptoms by Pearson correlation in the AR and pure AR groups. Our study demonstrated that the ADHD symptom score was higher in children with AR than in the controls. In addition, among children with AR, the more serious of the AR symptoms significantly increased ADHD-related scores (the subscales of CBCL and SNAP-IV). Several previous studies^{13,14,29} confirmed that children with untreated AR had higher ADHD scores than did the healthy controls. Some possible risk factors for ADHD symptoms in children with AR were explored in this study. Our results highlighted that the management of comorbid ADHD symptoms in children with AR should not only focus on their nasal symptoms but also monitor their neuropsychiatric symptoms.

Based on the analysis of the Pearson correlation results, it was observed that there was a clear positive correlation between PRQLQ and the subscales of CBCL and SNAP-IV. Moreover, significantly more ADHD-related behavioral problems (as revealed by the CBCL subscale that explores emotional instability and attentional problems) were observed in children with AR, which emphasized the possible relationship

between AR and ADHD. From the results of hierarchical regression analyses (Table 7), we detected that the subtests of PRQLQ were significant predictors of the SNAP-IV and CBCL. This was reliable evidence that emphasized the possible relationship between AR and ADHD. Previous studies reported the coexistence of ADHD, allergic disease,^{33,49} and allergic symptoms in ADHD patients.^{28,50} The results of our study regarding AR were consistent with some previous studies. For instance, Shyu *et al.*¹⁵ detected a relationship between the presence of AR and the development of ADHD in the National Health Insurance Database of Taiwan. Schieve *et al.*⁵¹ also reported a significantly high risk of ADHD presence in children with AR. However, the links between pediatric AR and ADHD remain poorly understood.

After the Pearson correlation analysis, we identified the basic variables (age, male sex, and environmental exposure to tobacco smoke) that may be responsible for the subscales of CBCL and SNAP-IV in both children with AR and healthy children. According to the literature,^{15,25} based on age, the odds ratios for ADHD in children with AR and children with other allergies were the highest in those children between 6 and 11 years of age, and decreased thereafter. Likewise, we found that age had a negative effect on ADHD scores among children with or children without AR. In terms of sex, boys are more likely to have ADHD³³ and are likely to be more impulsive than girls.^{22,52} Our results were similar to these findings. The influence of environmental exposure to tobacco smoke is complex,⁵³ and such exposure was strongly associated with inattention in one clinical study,⁵⁴ which was consistent with our results.

However, it should be noted that the relationship between AR and ADHD has not been clearly understood. Recently, many articles in the literature report the correlation between cognitive symptoms and AR. Some possible causes are presumed. AR affects the quality of sleep and causes daytime fatigue, cognitive, and memory disorders.^{55,56} Furthermore, AR is also associated with sinusitis, Eustachian tube dysfunction, and conductive hearing loss that may trigger learning disorders.⁵⁵ A considerable amount of pediatric AR has been associated with sleep disruption.⁹ It has been explored that poor quality of sleep may result in inattentive and impulsive behaviors at the field of neural circuitry and neurotransmitter systems.^{57,58}

The cortical and brainstem regions (consist of abnormalities in their frontal, ventrolateral prefrontal, dorsolateral prefrontal, and dorsal anterior cingulate cortices; the striatum and lateral temporal and parietal), which connects the major sites implicated in the pathophysiology of ADHD are associated with the regulation of attention and responsiveness to sleep deprivation.^{57,58} Furthermore, reduced connectivity and changed circuitry in key circuits that belong to sleep-dependent learning have been evidenced in ADHD⁵⁸, including disrupted limbic-prefrontal circuits (the ventral medial prefrontal cortex) and altered connections among prefrontal regions and the amygdala and the hippocampus.^{59–61} In addition, the neurotransmitter systems overlap in the regulation of attention and sleep deprivation. Recently, some animal, neuroimaging, pharmacologic, and genetic studies reported that ADHD is due to dysregulation of dopamine and norepinephrine.^{59,60,62}

Several other possible explanations of this relationship have been suggested. The autonomic nervous system and the hypothalamic-pituitary-adrenal axis link the brain to the immune system.⁶³ Psychological factors (emotions and stress) influence asthma systems *via* the autonomic nervous-vagal systems.^{64,65} These observations may explain the association between allergic disease and ADHD. The relationship between behavioral problems and the allergic disease-related variables remains poorly understood. However, our novel findings indicated that a positive relationship exists between atopy and behavioral problems in children.

Our study had several limitations. ADHD questionnaires were administered by trained experimenters rather than child psychiatrists, which might have affected the quality of our study. The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition⁶⁶ had not been used for diagnosing ADHD; thus, we could not establish a direct

diagnostic connection between ADHD and AR. Moreover, our diagnostic process was flawed, and appropriate follow-up is required to confirm an ADHD diagnosis. In addition, the educational and cooperation levels of parents varied. Even after excluding the low quality and incompleteness of the data, the accuracy of our findings may have been compromised. To the best of our knowledge, no previous work addressed the relationship between ADHD and AR by using objective and well-validated measures of both AR and behavioral problems in Chinese children and adolescents. Our current results indicated that further longitudinal studies on the relationships between allergic disease and behavior disorders in children and adolescents are required.

CONCLUSION

This study demonstrated that ADHD symptoms were common in children with AR, and the psychosocial behavior pattern varied with the allergic symptoms in play. We also found that there is a requirement of a comprehensive and specific management for pediatric allergic disorders with borderline ADHD symptoms, along with medical and psychosocial intervention. Further studies should assess the effects of medication and psychological treatment on children with ADHD and AR.

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