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Risk of bipolar disorder among adolescents with allergic rhinitis: A nationwide longitudinal study

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ABSTRACT

Background: Previous studies have suggested an immunological dysfunction in bipolar disorder, but none has investigated the temporal association between allergic rhinitis (AR) and bipolar disorder.
Methods: Using Taiwan National Health Insurance Research Database, 9506 adolescents aged 12–18 years with allergic rhinitis were enrolled between 2000 and 2008 and compared to 38,024 age-and gender-matched (1:4) control groups. Subjects of bipolar disorder that occurred up to the end of follow-up (December 31, 2011) were identified.
Results: Adolescents with AR had a significantly higher incidence of developing bipolar disorder (0.77 vs. 0.18 per 1000 person-years, $p < 0.001$) during the follow-up period than the controls. Adolescents with AR had an increased risk (hazard ratio [HR]: 4.62, 95% confidence interval [CI]: 3.17–6.75) of developing bipolar disorder in their later life compared to the control group after adjusting for demographic data and comorbid allergic diseases.
Discussion: This is the first study showing a temporal association between AR and bipolar disorder, in that patients who had AR in adolescence exhibited an increased risk of developing bipolar disorder in later life. Further study would be required to investigate the underlying mechanism about this association.

Allergic rhinitis (AR) is a common disorder that affects 10%–20% of the general population, mostly teenagers. AR is characterized by hypersensitivity symptoms, such as rhinorrhea, nasal obstruction or blockage, nasal itching, sneezing, and postnasal drip. The symptoms are induced by immunoglobulin-E (IgE)-mediated inflammation after the nasal mucous membranes are exposed to an allergen [14,23]. Although AR is not considered a severe disease and is usually ignored and underdiagnosed, it is detrimental to health and affects both the quality of life and productivity at work and school [4,14] and increases societal costs [4,14,23,24].

Evidence has shown that patients with AR may develop certain psychological problems. Bavbek et al. reported that patients with AR had significantly higher scores on all subscales of Symptom Checklist 90, particularly in the somatization and depression subscales, and lower scores of life satisfaction compared with the controls [2]. In a large-sample study of more than 85,000 individuals, Cuffel et al. revealed that patients with AR had a 1.7-fold higher chance of being diagnosed with depression than did the controls [10]. In addition, in a previous study, we suggested that AR in adolescence exhibited an increased risk of developing unipolar depressive disorder in later life after adjustment for comorbid allergic diseases [8,9]. Depression can be comorbid with AR, but whether AR triggers other severe mental disorders, such as bipolar disorder, remains unknown. A growing body of evidence indicates a possible association between immunological dysregulation, allergy, and bipolar disorder [3,12,13,17]. The early phase of an allergic response is predominantly mediated through Th_2 cytokines in which interleukin (IL)-4 and IL-13 drive the IgE production by promoting immunoglobulin class switch recombination in B cells. In addition, a cascade of proinflammatory agents, such as Th_1 immunoactive cytokines (ie, IL-2, IL-3, tumor-necrosis factor-α [TNF-α]) and chemokines are released sequentially [11]. These proinflammatory cytokines play a role in the pathophysiology of bipolar disorders [18,19,22,32]. Kim et al. studied the cell-mediated immune activation response in patients with bipolar disorder and showed that patients exhibited a significantly higher level of IL-6 and TNF-α and a higher ratio of TNF-α/IL-4, IL-2/IL-4, and IFN-γ/IL-4 than did the controls [18]. On assessing 23 patients

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with bipolar disorder and 23 controls, Tsai et al. found increased serum levels of soluble IL-2 receptor in patients with bipolar disorder [32]. However, large-scale epidemiological studies investigating the association of AR and bipolar disorder are scant.

In this study, we hypothesized that AR in adolescence increases the risk of bipolar disorder in later life, and conducted a case-controlled large-sample nationwide population-based longitudinal follow-up study. This longitudinal cohort study clarified the temporal relationship of AR with bipolar disorder.

Methods

Data source

The National Health Insurance (NHI) program was implemented in Taiwan in 1995, and covers up to 99% of all 23,000,000 residents of Taiwan at this time. The NHI Research Database (NHIRD) recorded the insured residents' demographic and medical information, including age, gender, residence location, prescription drugs, prescription date, and diagnosis. The International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) was used for the diagnosis. The completeness and accuracy of the NHIRD has been affirmed by the Department of Health and the Bureau of NHI through audit. The NHIRD has been used extensively in many epidemiologic studies in Taiwan [1, 6–9,20,33].

Inclusion criteria for the adolescents with AR and the control group

Adolescents aged between 12 and 18 years who had a diagnosis of AR (ICD-9-CM code: 477) given by internists, family physicians, or pediatricians and no history of psychiatric disorders (ICD-9-CM code: 290–319) before enrollment between January 1, 2000 and December 31, 2008, were included in our study. The age-, gender, and enrollment time-matched control group (4 for every patient in the study cohort) was randomly identified from among the subjects after eliminating adolescents who had been given a diagnosis of AR anytime and those who had any psychiatric disorder before enrollment. The subjects identified as having bipolar disorder (ICD-9-CM codes: 296.0, 296.1, 296.4, 296.5, 296.6, 296.7, 296.80, 296.81, 296.89) during the follow-up were given at least twice by the board-certificated psychiatrists based on their clinical judgment. Because of the high comorbidity of other allergic diseases with AR, comorbid allergic diseases, including asthma (ICD-9-CM codes: 493, 493.0, 493.1, or 493.9), diagnosed by internists, pulmonologists, rheumatologists, or pediatricians, and atopic dermatitis (ICD-9-CM codes: 691 or 691.8) diagnosed by dermatologists or pediatricians, were identified. Level of urbanization based on the post code (level 1 to level 5; level 1: most urbanized region; level 5: least urbanized region) was also assessed in our study. The urbanization index (most urbanized region to the most rural region) developed by the National Health Research Institute, Taiwan [21].

Statistical analysis

For between-group comparisons, the independent t test was used for continuous variables and Pearson's X^2 test for nominal variables, where appropriate. The Cox regression model was used to investigate the HR with 95% CI of bipolar disorder after adjusting for demographic data and comorbid allergic diseases. A two-tailed p-value of less than 0.05 was considered statistically significant. All data processing and statistical analyses were performed with Statistical Package for Social Science (SPSS) version 17 software (SPSS Inc) and Statistical Analysis Software (SAS) version 9.1 (SAS Institute, Cary, NC).

Results

Demographic characteristics of patients with allergic rhinitis and the control group

In all, 9506 adolescents with AR (49.3% for males and 50.7% for females) and 38,024 controls at a mean age of 14.81 years were included in our study. Adolescents with AR had a higher incidence of developing bipolar disorder (0.77 vs. 0.18 per 1000 person-years) with an earlier age onset of disease (20.03 ± 3.22 vs. 22.31 ± 3.01, $p < 0.001$) during the follow-up period than in the control group (Table 1). Among patients with bipolar disorder, 27 males and 32 females were in AR group and 17 males and 38 females were in the control group ($p = 0.125$). In addition, the prevalence of comorbid allergic diseases, including asthma (17.4% vs. 2.4%, $p < 0.001$) and atopic dermatitis (4.2% vs. 1.6%, $p < 0.001$), in the AR patient group was significantly higher than that in the control group (Table 1). Adolescents with AR resided more in urbanized region ($p < 0.001$) and had a lower income ($p < 0.001$) (Table 1).

Hazard ratio for bipolar disorder

Three Cox regression models were used to examine the risk of developing bipolar disorder among AR patients compared to the controls: the first model to calculate the crude HR, the second model to calculate the adjusted HR after controlling age, sex, income, and level of urbanization, and the third model to calculate the adjusted HR controlling age, sex, income, level of urbanization, and allergic comorbidities. Three models showed a consistent finding that adolescents with AR were prone to developing bipolar disorder in later life (crude HR: 4.29, 95% CI: 2.97–6.19; adjusted HR in second model: 4.37, 95% CI: 3.03–6.33; adjusted HR in third model: 4.62, 95% CI: 3.17–6.75) (Table 2). The survival curve of adolescents with bipolar disorder with or without AR can be seen in Fig. 1.

Discussion

Our study is the first to investigate the temporal association of AR and bipolar disorder. The study results, after adjustment for other

Table 1
Distribution of characteristics of subjects with allergic rhinitis and control group.

	Adolescents with allergic rhinitis (n = 9506)	Controls (n = 38,024)	p value
Gender (male, n, %)	4683 (49.3)	18,732 (49.3)	–
Age at allergic rhinitis diagnosis or enrollment (year, SD)	14.81 (2.1)	14.81 (2.1)	–
Bipolar disorder (n, per 1000 person-years)	59 (0.77)	55 (0.18)	<0.001
Age at diagnosis (years, SD)	20.03 (3.22)	22.31 (3.01)	<0.001
Duration between enrollment and bipolar diagnosis (years, SD)	5.00 (2.38)	6.42 (2.95)	<0.001
Allergic comorbidities (n, %)			
Asthma	1655 (17.4)	923 (2.4)	<0.001
Atopic dermatitis	401 (4.2)	597 (1.6)	<0.001
Level of urbanization (n, %)			<0.001
1 (most urban)	3175 (33.4)	11,383 (29.9)	
2	2975 (31.3)	11,606 (30.5)	
3	1611 (16.9)	7186 (18.9)	
4	1155 (12.2)	5048 (13.3)	
5 (most rural)	590 (6.2)	2801 (7.4)	
Income-related insured amount			<0.001
≤15,840 NTD/month	6046 (63.6)	22,393 (58.9)	
15,841–25,000 NTD/month	2279 (24.0)	11,799 (31.0)	
≥25,001 NTD/month	1181 (2.5)	3832 (10.1)	

SD: standard deviation; NTD: New Taiwan Dollar.