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Original Article

The Association between Allergic Rhinitis and Schizophrenia in the North of Iran: a large scale, population based cross-sectional study

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ABSTRACT

Background: The literature indicates a link between schizophrenia and a disturbance in innate and adaptive immunity. However, the results about allergic rhinitis have been inconsistent so far. The aim of this population-based study was to investigate the prevalence and clinical features of allergic rhinitis in patients with schizophrenia.

Methods: This cross-sectional study was performed on 998 patients and 1000 age- and sex-matched control subjects from March 2013 to August 2014. All participants were assessed by the Score for Allergic Rhinitis (SFAR) questionnaire and nasal smear (for eosinophilia) investigation. Symptoms were assessed using the Brief Psychiatric Rating Scale (BPRS). Univariable and multivariable logistic regression models were fitted to estimate adjusted odds ratios.

Results: The mean age of subjects was 45.0 years, and 61.0% of subjects of either group were male. About 26.5% of subjects in the case group and 21.0% in the control group had allergic rhinitis. The patients with schizophrenia were found to be at an increased risk for allergic rhinitis (adjusted OR 1.41, 95% CI 1.08-1.83) compared to control subjects. Furthermore, multivariable logistic regression identified the affect subscale on the BPRS as a risk factor of allergic rhinitis (P=0.004).

Conclusion: Our results suggest that the prevalence of allergic rhinitis is higher in patients with schizophrenia. However, the impact of type and severity of allergic rhinitis on the course of schizophrenia must be investigated in further trials.

Keywords: Allergic rhinitis, Association, Atopic disorder, Prevalence, Schizophrenia

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Introduction

Schizophrenia is a severe and chronic mental disorder that affects approximately one percent of the general population globally (1). Several hypotheses have been proposed to explain the neurodegenerative and abnormal neurodevelopmental processes underlying the pathogenesis of schizophrenia. One hypothesis posits that inflammatory disturbances may contribute to the etiology of schizophrenia. Complex interactions between the immune system and the brain have been implicated in the pathophysiology of several psychiatric disorders (2). Several epidemiological studies have reported an increased risk for schizophrenia among those with autoimmune disorders and/or severe infections (3-5).

Although several studies showed higher prevalence rate of asthma in schizophrenia patients (6-9), the current literature on the association of allergic rhinitis (AR) with schizophrenia is relatively sparse and the results are contradictory. Chen *et al.* (2009) analyzed data from the Taiwan National Health Insurance Research Database for the years 2000 to 2002 and found a reduced prevalence rate of AR among schizophrenia patients. The authors argue that since AR is not life-threatening, its reduced incidence may be due to financial costs and under-use of medical treatment (6). Pedersen *et al.* (2012) conducted a population- based cohort study in Danish population and revealed an insignificant rate ratio for AR. However, when atopic dermatitis, urticaria and AR were collapsed into one group, a significant risk factor [1.27 (95% CI: 1.00–1.58)] was observed in the crude model (7). In contrast with these studies, Okusaga *et al*. (2014) reported that the prevalence of atopy is lower in patients with schizophrenia using the Phadiatop multiallergen screen (8). Regarding to the heterogeneity of the results, we conducted a cross sectional study to explore the association between schizophrenia and AR.

Materials and Methods

The present study was a population-based, cross-sectional survey on patients with mental health disorder seeking medical management services at the local primary health care system (PHC) from March 2014 to August 2015. A total of 1074 patients with schizophrenia were recruited from 16 Health centers in Guilan province, Iran. All the study subjects signed informed consent forms prior to the participation in the study. For participants without decision-making capacity, the primary caregiver gave permission on behalf of the participant. The study protocol was approved by the review boards of Guilan University of Medical Sciences (approval id: IR.GUMS.REC.1394.782) and complied with the principles outlined in the Helsinki Declaration.

There were no specific exclusion criteria. After considering inclusion criteria, 998 subjects with schizophrenia were selected as the case group. The control group was selected randomly from age- and sex-matched subjects seeking medical management services at the primary health care (PHC) centers and had no history of psychiatric problems.

The diagnosis of schizophrenia was based on DSM-IV (10) and made by psychiatrists at the PHC centers. Demographic data, as well as clinical and treatment-related details were collected. The Brief Psychiatric Rating Scale (BPRS) was used to measure the presence and severity of psychopathology (11). Patients were asked to complete the score for allergic rhinitis (SFAR) questionnaire to assess their AR status. This scale includes main symptoms of AR such as blocked nose, runny nose, sneezing, and itchy eyes, as well as the related factors. The final score of the SFAR ranges from 0 to 16 (12). Annesi-Maesano *et al.* (2002) validated the SFAR and showed that a score ≥ 7 optimally discriminates between individuals with AR and those without (13).

The nasal cavity was examined by a general physician through the use of anterior rhinoscopy (nasal speculum). Color (bluish or whitish) and swelling of the mucosa, the presence of nasal wetness, and transverse crease of the external nose were evaluated. In order to take a nasal smear for tissue eosinophilia, the patients were asked to stop their medications (antihistamine and/or nasal corticosteroids) for at least 5 days before taking the nasal smears. A straight cotton swab along the base of the nose was passed under the inferior turbinate and twisted. The smear was then air-dried on a glass slide and fixed with 95% alcohol immediately. The slides were stained with Wright-Giemsa stain, and examined under a light microscopy using a × 40 power objective. The eosinophil count was expressed as the percentage of the total cells. A smear was considered positive for eosinophilia when there were 5% eosinophils out of total leukocytes (14).

Statistical analysis

We presented frequencies for categorical variables and mean and standard deviation for continuous variable. We performed subsequent subgroup analyses in terms of sex and age group. Univariable logistic regression models were applied to assess the relationship between potential predictor variables and outcome of AR in schizophrenic patients. Variables significant at the 10% level were entered into multivariable logistic regression models. In a next step, any variables not significant at the 5% level were removed so that only variables significant at the 5% level remained in the final model. Crude and adjusted odds ratios are reported with 95% confidence intervals and P values. All data were analyzed using SPSS 19.0 (IBM, SPSS, Inc., Chicago, IL, USA). Statistical significance was set at $P < 0.05$.

Results

A total of 998 patients with schizphrenia and 1000 control subjects participated in the present study. The mean age of participants was 45.0 years, and 61.6% of patients with schizophrenia and 56.3% of control subjects were male. The frequency of smoking in the schizophrenic patients was significantly more compared to controls (49.3% versus 15.3%, respectively). The baseline characteristics of all subjects are summarized in Table 1.

Table 1. Characteristics of the study population

	Control subjects (n=1000) Mean (SD) or Percent	Schizophrenic patients (n = 998) Mean (SD) or Percent
Age, y	44.9 (12.6)	45.1 (12.1)
Sex		
Male	56.3	61.6
Female	43.7	38.4
Marital status		
Single	13.0	46.7
Married	83.9	45.1
Widowed	3.1	8.2
Socioeconomic status		
Low	49.3	87.0
High	50.7	13.0
Education level		
Illiterate	32.5	49.6
Elementary	38.7	32.1
Secondary	25.1	16.4
Tertiary	3.7	1.9
Smoking	15.3	49.3
Duration of illness, y		16.5 (9.2)
BPRS		
Total		52.9 (21.7)
Affect		12.5 (5.2)
Positive		11.7 (5.9)
Negative		10.8 (5.2)
Resistance		8.7 (5.1)
Activation		9.3 (5.3)
Chlorpromazine-equivalent dose, mg		251.8 (242.7)
Antipsychotic drug		
Total		79.2
Typical		37.9
Atypical		29.3
Both		11.9

In the schizophrenic patients, 265 (26.6%) were diagnosed with AR. Also, 210 (21.0%) of 1000 healthy controls had AR. After adjusting for marital status, socioeconomic status, education level, and smoking, the results showed that the schizophrenic patients were at an increased risk of AR (OR 1.41, 95% CI 1.08-1.83) compared with control subjects. After subgroup analysis, in the case group, male sex and age $\geq$ 45 years were associated with AR significantly (Table 2). AR prevalence was slightly higher in males (27.0%) than that in females (26.0%).

Table 2. Subgroup analyses of the association between allergic rhinitis and schizophrenic disorder by age and sex

	Adjusted OR (95% CI)*	P value
Male		
Healthy control	Reference	
Schizophrenic patients	1.60 (1.11-2.30)	0.01
Female		
Healthy control	Reference	
Schizophrenic patients	1.24 (0.83-1.85)	0.31
Age < 45y		
Healthy control	Reference	
Schizophrenic patients	1.32 (0.88-1.99)	0.18
Age ≥ 45y		
Healthy control	Reference	
Schizophrenic patients	1.47 (1.03-2.10)	0.03

OR: odds ratio; CI: confidence interval.
* Adjusted by marital status, socioeconomic status, education level, and smoking.

Then, we evaluated the effects of profile of schizophrenia on the risk of AR. As shown in Table 3, patients with higher score of the affect, positive and negative subscales or higher total score in BPRS always had higher risk of AR. However multivariable logistic regression identified only the affect subscale as a risk factor of AR (P = 0.004). The duration of illness and the type or dosage of antipsychotics were not significantly associated with AR.

Table 3. Univariable and multivariable associations of BPRS symptoms and some clinical findings with allergic rhinitis in the schizophrenic patients

	Patients with allergic rhinitis Mean (SD) or Percent	Patients without allergic rhinitis Mean (SD) or Percent	Univariable analysis		Multivariable analysis*	
			Crude OR (95%CI)	P value	Adjusted OR (95%CI)	P value
Duration of illness, y	16.1 (8.7)	16.6 (9.4)	0.99 (0.98-1.01)	0.48	0.99 (.97-1.02)	0.47
Symptoms on BPRS						
Total	56.2 (18.2)	51.7 (22.8)	1.01 (1.00-1.02)	0.02	0.95 (0.89-1.03)	0.19
Affect	14.1 (4.4)	11.9 (5.4)	1.08 (1.05-1.12)	<0.001	1.15 (1.05-1.26)	0.004
Positive	12.4 (5.1)	11.4 (6.2)	1.03 (1.00-1.06)	0.02	1.08 (0.96-1.22)	0.18
Negative	11.5 (4.7)	10.6 (5.4)	1.03 (1.01-1.07)	0.02	1.04 (0.95-1.16)	0.41
Resistance	9.1 (4.3)	8.5 (5.3)	1.06 (0.96-1.16)	0.23	1.05 (0.94-1.16)	0.41
Activation	9.6 (4.0)	9.3 (5.7)	1.01 (0.98-1.04)	0.42	1.04 (0.95-1.13)	0.31
Chlorpromazine-equivalent dose, mg	225.9 (204.8)	260.4 (254.4)	1.00	0.07	1.00	0.42
Antipsychotic drug						
None	22.3	20.1	1	0.83	1	0.89
Typical	36.7	38.8	0.85 (0.57-1.29)	0.45	1.14 (0.64-2.01)	0.66
Atypical	30.1	29.0	0.94 (0.61-1.44)	0.78	1.26 (0.69-2.30)	0.46
Both	10.9	12.2	0.81 (0.46-1.41)	0.45	1.10 (0.50-2.44)	0.82

OR: odds ratio; CI: confidence interval.
* Adjusted by marital status, socioeconomic status, education level, and smoking.

Discussion

The present study revealed a high prevalence of AR among healthy controls and schizophrenic patients in the North of Iran. The prevalence of AR in healthy controls (21.0%) was similar to the results of previous studies in Iran (15, 16). This study indicates a higher prevalence of AR in the patients with schizophrenia compared to healthy controls. The schizophrenic patients had 41% more odds of AR than controls. The odds of AR were significantly more in the male and age ≥ 45 years subgroups. There was a significant relationship between AR and affect subscales on BPRS. The affect subscale consists of anxiety, guilt feelings, depressive mood, and somatic concern.

Although about fifty percent of schizophrenic patients were smokers which was significantly higher than this rate in controls, the association between AR and schizophrenia was adjusted for this potential confounder. Saulyte *et al.* (2014) reported no significant association between active smoking and the risk of AR and found that increased nasal response to allergen in children and adolescents by smoking is a transient effect and sensitization to tobacco is mitigated by increasing age (17).

In subgroup analysis, the risk of AR was higher among older patients, which could be due to the confounding effect of other factors such as duration of illness or severity of schizophrenia. Allergic rhinitis appeared to be slightly higher in

males than females which was similar to finding of An's *et al.* (18). The majority of patients with AR in the present study had lower socioeconomic status and education level, compared to control subjects. An *et al*. (2015) hypothesized that today, those who obtain higher education and enjoy a high income usually work in jobs featuring more indoor than outdoor activity.

In one prior study, patients with urticaria demonstrated significantly higher scores for schizophrenia, paranoia, and psychopathic deviance, compared with healthy controls (19). Lv *et al.* (2010) found poorer psychological functioning in women with moderate to severe persistent AR than non-allergic women (20). The researchers showed that skin prick test scores were positively correlated with several scores, especially schizophrenia, in personality trait assessment. Recently, Begemann *et al.* (2019) found an increased risk of psychotic experiences in patients with atopic disorders as compared with controls (OR 1.26) in a Dutch population sample. The ORs were highest for allergic rhinitis (1.46), followed by asthma (1.32), and eczema (1.20). These results provided further support for the involvement of immunological processes in the pathophysiology of psychosis (21).

It has been proposed that cytokine regulation disturbances play a substantial role in the pathogenesis of both schizophrenia and such dermatologic disorders. Chiang *et al*. (2013) showed an imbalance between T-helper type 1 (Th1) and type 2 (Th2) cytokines in favor of Th2 shift which appeared to be specific for schizophrenia (22). Th1 cells are known to be involved in cellular immunity against intracellular bacteria and viruses and in autoimmune diseases such as multiple sclerosis and rheumatoid arthritis. In contrast, Th2 cells manage humoral immunity against extra-cellular parasites and allergic reactions (23, 24). The higher prevalence of allergic rhinitis, a so-called Th2 disease, in patients with schizophrenia versus control subjects could be regarded as support for the Th1/Th2 imbalance hypothesis. Although elevated peripheral cytokine levels are not necessarily associated with inflammation of the CNS, inflammation of the CNS (neuroinflammation) is an important factor in the etiology of schizophrenia. It is possible for cytokines to cross the blood brain barrier (BBB) by several mechanisms such as saturable transport, disruption of the BBB, and through circumventricular organs that lack the BBB (23). Our finding requires further investigation, and if replicated, they have implications for our understanding of the differential mechanisms which are at play in the etiology of schizophrenia. Shared genetic factors potentially link AR and schizophrenia.

It is merit to note some limitations of this study. First, the diagnoses of AR in our study were based on SFAR questionnaire and nasal smear. Due to the absence of biological measures of AR (such as a skin prick test or an IgE-test), some of the subjects may have been incorrectly categorized and the results may be less evident. However, previous studies have reported a good correlation between clinical diagnosis and specific IgE against inhaled allergens (25). Second, because we did not recruit a control group with other (non-schizophrenia) psychiatric disorders, it is not possible to distinguish whether the results are specific to schizophrenic patients or applicable to psychiatric patients in general. Third, since the present analysis is cross-sectional, clear establishment of the sequence of events is not possible.

Conclusion

In conclusion, this study provided the first evidence for the prevalence of AR in patients with schizophrenia. Replication of these results is needed to confirm the associations between schizophrenia and atopic disorders. As for clinical implications, psychiatrists should be more aware of detecting and treating physical comorbidities common among schizophrenia patients, including AR as part of an effective management of the disease. Future studies on the identification of common etiologic pathways for these two diseases could be clinically significant for developing innovative treatment targeting both illnesses concurrently. Finally, longitudinal studies that can investigate the sequence of onset and the effects of biological, psychosocial and environmental risk factors in the association between schizophrenia and AR are needed to illuminate possible shared etiopathogenesis mechanisms.

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The study protocol was approved by the review board of Guilan University of Medical Sciences (approval id: IR.GUMS.REC.1394.782) and complied with the principles outlined in the Helsinki

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Authors' contribution

Robabeh Soleimani contributed in the conception of the work, analysis and interpretation of data, drafting the work, final approval of the final version of the manuscript, and agreed for all aspects of the work. Mir Mohammad Jalali contributed in the design of the work, drafting and revising the draft, approval of the final version of the manuscript, and agreed for all aspects of the work. Shahin Baftehchi contributed in the acquisition of data for the work, revising the draft, approval of the final version of the manuscript, and agreed for all aspects of the work. Mahnaz Fallahi Khesht Masjedi contributed in the acquisition of data for the work, revising the draft, approval of the final version of the manuscript, and agreed for all aspects of the work.

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