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Correlations of thyroid autoantibodies with allergic diseases

A case-control study of 434 Chinese patients

Congcong Zhang, MM[a], Chengwei Hong, MM[a], Xiaolan Lian, MD[a], Liping Wen, MD[a], Kun Xu, MM[a], Zhuang Tian, MD[a], Wenjie Si, MM[a], Yongning Li, MD[a,*]

Abstract

There is growing interest in the relationship between allergies and autoimmune diseases, although previous studies have yielded inconsistent results.

The thyroglobulin (Tg)/thyroid peroxidase antibody (TPOAb) group consisted of 217 patients with positive thyroglobulin antibody (TgAb) and/or TPOAb test results. Another set of 217 age- and sex-matched individuals with both TgAb- and TPOAb-negative results were selected as control group. History of allergic rhinitis (AR), chronic spontaneous urticaria (CSU), and/or atopic dermatitis (AD) was elicited before autoantibody detection. The association of thyroid autoantibodies with allergic diseases was assessed using univariate and multivariate logistic regression analysis, and the results were reported as odds ratios (ORs).

TgAb positivity (OR, 2.333) was identified as a risk factor for AR, AD, or CSU in Chinese patients, suggesting the involvement of thyroid autoantibodies in the pathogenesis of atopic reactions. Multivariate regression analysis also confirmed that the presence of TgAb (P = .004), rather than TPOAb (P = .468), had a significant impact on the occurrence of allergic disease.

Physicians should carefully monitor atopic symptoms in individuals with elevated TgAb or TPOAb levels to reduce the risk of allergic diseases, such as AR, AD, and CSU.

Abbreviations: AD = atopic dermatitis, AITD = Autoimmune thyroid disease, AR = allergic rhinitis, CSU = chronic spontaneous urticaria, FT = free thyroxine, GD = Graves disease, HT = Hashimoto thyroiditis, ORs = odds ratios, T = thyroxine, TgAb = thyroglobulin antibody, TSH = thyroid stimulating hormone, TPOAb = thyroid peroxidase antibody.

Keywords: allergic rhinitis, atopic dermatitis, autoimmune diseases, chronic spontaneous urticarial, thyroglobulin antibody, thyroid peroxidase antibody

1. Introduction

Hypersensitivity reactions of the immune system are classified as atopic allergies or autoimmune reactions based on the origin of the antigen (endogenous or exogenous), the type of immune response involved (cellular and humoral), and the clinical symptoms.[1] Allergies and autoimmune diseases are the 2 potential outcomes of hypersensitivity, and the relationship between the 2 has been a research hotspot, especially in the context of common atopic allergies that significantly affect the daily life of patients, such as allergic rhinitis (AR), chronic spontaneous urticaria (CSU), and atopic dermatitis (AD).[2] For example, nasal mucosa inflammation in AR has been shown to be mediated by immunoglobulin E and a variety of immunocompetent cells and cytokines.[3–5] Studies have demonstrated that helper T cells 2 (Th2) in the nasal mucosa play a dominant role in the pathogenesis of AR, causing Th1/Th2 immune imbalance.[6–9] The cause of CSU is unknown, but ≈30% to 40% of patients have an underlying autoimmune pathology.[10–12] The causation of AD is believed to involve genetic, environmental, skin barrier, and immune interactions, including Th1/Th2 cellular immune imbalance.[13–15]

One of the most prominent organs affected by autoimmune diseases is the thyroid gland. Autoimmune thyroid disease (AITD) refers to an immune attack on the thyroid due to a disorder of the immune system[16] and mainly includes Graves disease (GD) and Hashimoto thyroiditis (HT). The estimated global prevalence of AITD is approximately 5% and varies according to sex (high prevalence in women), age (high prevalence in elderly patients), race, geography, diet, genetics, and other factors.[16,17] Both GD and HT can be caused by tissue damage and thyroid dysfunction induced by thyroid tissue autoantibodies-mediated antibody-dependent cellular cytotoxicity.[18] In addition, several

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The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Our research complied with the guidelines for human studies and was conducted ethically in accordance with the principles enshrined in the World Medical Association Declaration of Helsinki. Written informed consent was obtained from all patients and the study protocol was approved by the Peking Union Medical College Hospital's committee on human research (No: S-K 1558).

[a] Department of International Medical Services, Peking Union Medical College Hospital, Beijing, China.

**Correspondence: Yongning Li, Department of International Medical Services, Peking Union Medical College Hospital, NO.1 Shuaifuyuan, Dongcheng District, Beijing 100730, China (e-mail: liyongning@pumch.cn).*

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recent studies have shown that the prevalence of 2 major thyroid autoantibodies, thyroglobulin antibody (TgAb) and thyroid peroxidase antibody (TPOAb), may have a certain correlation with the occurrence of AR, CSU, AD, and other allergic diseases due to the common underlying pathogenic mechanisms.[6,19,20]

However, most previous studies have only focused on the correlation between TgAb or TPOAb and a single allergic disease, and there is a paucity of studies conducted in the Chinese population. Studying the relationship of AITD with the 3 allergic diseases mentioned above in the Chinese population will facilitate better characterization of AITD and allergic diseases, with the goal of directing prevention, screening, and treatment. In this study conducted at the Health Management Center of the Peking Union Medical College Hospital, we adopted a case-control design to obtain the clinical information of patients with positive (Tg/TPOAb group) or negative (control group) TgAb or TPOAb test results. Both groups were matched with respect to age and sex in a 1:1 ratio. The subjects were further questioned about their history of AR, CSU, and/or AD before autoantibody detection so as to evaluate the correlation between allergic diseases and thyroid autoantibodies.

2. Materials and Methods

2.1. Study subjects

The geographic and clinical data, including sex, age, height, weight, blood pressure, blood routine test, and blood sugar were retrieved from the electronic medical records from January 2018 to June 2020 at the health management center of our hospital. The inclusion criteria were (1) age > 18 years; (2) TgAb or TPOAb test was explicitly positive or negative; (3) provision of written informed consent for participation in the study. Our research complied with the guidelines for human studies and was conducted ethically in accordance with the principles enshrined in the World Medical Association Declaration of Helsinki. The study protocol was approved by the Peking Union Medical College Hospital's committee on human research (No: S-K 1558).

2.1.1. TgAb or TPOAb test. Three milliliters of peripheral venous blood that was routinely drawn from the research subjects was placed in a sterile desiccant tube at room temperature for 30 minutes, followed by centrifugation at 2400 rpm for 5 minutes. Serum was used to detect TgAb and TPOAb with the immunochemiluminescence method. The normal range of TPOAb and TgAb is 0 to 35 IU/mL and 0 to 40 IU/mL, respectively. A measured value greater than the upper limit of the normal range was defined as TPOAb or TgAb positive. The exclusion criteria were (1) post-thyroidectomy; (2) history of malignant tumors or other autoimmune diseases; (3) severe cardiovascular and cerebrovascular disorders (such as stroke and myocardial infarction) and/or dysfunction of the liver or kidney; (4) participated in other clinical studies before the TgAb or TPOAb tests; (5) pregnant or lactating women.

Individuals who qualified the above criteria were subjected to further inquiries: (1) history of AR, CSU, AD, hypertension, or diabetes; (2) frequency and severity of AR, CSU, and AD within 1 month before the physical examination (rated by the patient: 0 score means no symptoms and 10 points means the highest frequency of attacks and the most severe symptoms); (3) usage of antihypertensive medications, hypoglycemic agents, local/systemic glucocorticoids, or local/systemic antihistamines.

The diagnostic criteria for AR are 1) 2 or more symptoms, such as sneezing, clear watery nasal discharge, nasal congestion, nasal itching, itchy eyes, or conjunctival congestion, that last or worsen for > 1 hour each day and are accompanied by pale nasal mucosa, edema, or nasal watery secretion. 2) Skin prick test for allergens, serum-specific immunoglobulin E (IgE), or a nasal provocation test was positive. The diagnostic criteria for AD are 1) family history of allergies such as AR, allergic asthma, or other allergic conditions; 2) dry skin, thin texture, erythema, papules, or desquamation. 3) protracted disease course with recurrent attacks. CSU refers to transient inflammatory congestion and edema of the skin, mucous membrane, and blood vessels caused by a variety of factors. The diagnosis is made based on the clinical manifestations, which include the episodic occurrence of wind masses and plaques on the trunk, face, or extremities, with onset ranging from several times a day to once every few days, and a total disease duration of > 6 weeks.

2.2. Statistical analysis

SPSS 20.0 statistical software was used for analysis. Normally distributed continuous variables are described as mean ± standard deviation, whereas non-normally distributed continuous variables are described as median (first and third quartiles). Categorical variables are expressed as frequency (percentage). Between-group differences with respect to continuous variables were assessed using the independent sample *t* test or Mann–Whitney *U* test, whereas those with respect to categorical variables were assessed using the chi-squared test or exact probability method. The Tg/TPOAb group and the control group were matched 1:1 for age and sex to compare the differences in indicators between the 2 groups. The odds ratios (ORs) of thyroid autoantibody positivity for allergic diseases were analyzed using univariate and multivariate logistic regression analysis.

3. Results

3.1. General characteristics of the study population

Among the 1750 individuals admitted to the health management center of our hospital from January 2018 to June 2020,

Table 1

Basic characteristics and autoantibody levels in the study cohort.

Parameters	Tg/TPOAb–positive group (n = 217)	TgAb and TPOAb–negative group (n = 217)	*P* value
Age (years)	54.49 (11.48)	56.08 (11.86)	.155
Sex (male)	217/91	217/91	1.000
Hypertension prevalence (%)	18%	24%	.125
Diabetes prevalence (%)	11%	9%	.516
TPOAb (μIU/mL)	147.76 (162.82)	10.31 (4.44)	<.0001
TgAb (μIU/mL)	401.69 (772.08)	14.30 (13.46)	<.0001
TSH (μIU/mL)	2.56 (2.36)	1.88 (1.25)	<.0001
FT3 (ng/dL)	3.11 (0.91)	3.09 (0.50)	.741
FT4 (ng/dL)	1.23 (0.34)	1.17 (0.18)	.031
T3 (ng/dL)	1.08 (0.30)	1.08 (0.21)	.86
T4 (ng/dL)	7.60 (1.85)	7.60 (1.64)	.996

FT = free thyroxine, T = thyroxine, TgAb = thyroglobulin antibody, TPOAb = thyroid peroxidase antibody, TSH = thyroid stimulating hormone.

217 patients (91 men and 126 women; mean age 54 ± 11 years) were found to be positive for TgAb and/or TPOAb (Tg/TPOAb group) (Table 1). Among these, 38 patients had hypertension (18%), and 23 patients had diabetes (11%). Additionally, 217 matched control individuals (91 men and 126 women; mean age: 56 ± 12 years) who were both TgAb- and TPOAb-negative were randomly selected from the remaining 1533 individuals. These included 52 cases of hypertension (24%) and 20 cases of diabetes (9%). The TgAb and TPOAb levels in the Tg/TPOAb group were significantly higher than that in the control group ($P < .0001$), with comparable thyroxine 3 (T3), T4, free thyroxine 3 (FT3), and FT4 values, but not thyroid stimulating hormone (Table 1).

3.2. Association of TgAb or TPOAb with allergic diseases

Ten men and 17 women with allergic diseases were found in the Tg/TPOAb group (18 with AR, 5 with CSU, and 4 with AD). The control group had 11 men and 6 women with allergic diseases (11 with AR, 4 with CSU, and 2 with AD).

First, we performed univariate analysis to identify the potential variables associated with allergic diseases. Among the variables sex, TPO Ab, TgAb, hypertension, and diabetes, only the presence of TgAb was associated with the occurrence of allergic disease (OR, 2.333, 95% CI, 1.243–4.378) (Table 2). This indicated that the presence of thyroid autoantibodies is a potential risk factor for AR, AD, or CSU in Chinese patients.

Next, multivariate logistic regression analysis was performed to further identify the potential independent risk factors for allergic diseases. The variables sex, age, TPO Ab, TgAb, hypertension, and diabetes were included in the regression model. As shown in Table 3, the *P* values for sex ($P = .209$), age ($P = .455$), hypertension ($P = .971$), diabetes ($P = .477$), and TPO Ab positivity ($P = .468$) were all > 0.05, suggesting that no significant impact of these variables on the occurrence of allergic diseases; however, the presence of TgAb ($P = .004$) showed a significant association with the occurrence of allergic disease.

4. Discussion

Several recent studies have found a linkage of AITD with AR, CSU, and AD. Reisacher et al found that the incidence of AITD in AR patients (10.4%) was higher than that in patients without AR (9.9%).[21] In the study by Degirmenci et al,[6] the incidence of HT in the healthy control group was 1.5% as compared to 16.3% in the AR group. Amino et al[22] found that patients with AR had a higher positive rate for thyroid autoantibodies. A recent meta-analysis of 20 independent case-control studies found that the presence of thyroid autoantibodies in urticaria patients was significantly higher than that in the control group,[23] suggesting a potential association between CSU and AITD. The same conclusion was also reached by Chiu et al[24] based on a clinical study in Taiwan, China. In the study by Pedulla et al,[20] the prevalence of AITD in AD patients was significantly higher than that in healthy controls (9.52% vs 0%), and the prevalence of AITD in IgE-mediated AD patients was significantly higher than that in non-IgE–mediated AD patients (18.51 % vs 4.3%). However, a study by Wu et al[25] in Taiwan, China found no significant correlation between AD and AITD. The conflicting results in previous studies are likely attributable to the heterogeneity with respect to characteristics of the study population, such as age and race. Therefore, further clinical research to characterize the relationship between AD and AITD is a key imperative.[26]

The association between thyroid autoantibodies and allergic diseases has been investigated among populations of different countries. A study conducted in Thailand compared the prevalence of thyroid antibodies in 100 patients with CSU and 100 age- and sex-matched healthy volunteers.[27] The frequency of thyroid antibodies in the CSU group was significantly greater than that in the control group (21% vs 9%). A study conducted in Egypt by El Shabrawy et al[28] found no significant difference between adult patients with AR and/or bronchial asthma (n = 50) and controls (n = 50) with respect to the serum levels of T3, T4, or thyroid stimulating hormone. However, the mean serum anti-TPO level in patients was significantly higher than that in controls and showed a positive correlation with body mass index, age, and diastolic blood pressure. Their findings suggested a higher prevalence of hidden autoimmune thyroiditis in allergic patients than in the control group. To assess the potential association between atopy and thyroid autoimmunity (TA) in South Italian children affected by skin disease, Pedullà et al[29] conducted a study of 324 consecutive children who were referred to the Pediatric Department due to skin disease symptoms. As TA was diagnosed based on serum TgAb and TPOAb levels more than twice the normal values, they found a significantly higher prevalence of TA in atopics compared with nonatopics. In a study conducted by Kim et al[19] in Korea, female patients had a significantly higher risk of CSU compared to male patients, and those with AR and AD had a significantly higher risk of CSU compared to patients without respective diseases.

However, to the best of our knowledge, no previous study has compared the thyroid autoantibodies level between Chinese patients with AR, AD, or CSU and their age- and sex-matched controls. Our findings demonstrated a significant association between the presence of TgAb rather than TPOAb on the occurrence of allergic disease. Risk factor analysis also

Table 2

Identification of potential risk factors associated with allergic diseases.

	Odds ratio	95% confidence interval	
Sex (M/F)	0.770	0.412	1.439
TPO Ab(positive/negative)	1.067	0.558	2.041
TgAb(positive/negative)	2.333	1.243	4.378
Hypertension(without/with)	0.835	0.374	1.865
Diabetes(without/with)	0.640	0.190	2.162

F = female, M = male, TgAb = thyroglobulin antibody, TPOAb = thyroid peroxidase antibody.

Table 3

Results of multivariate logistic regression analysis showing association of TgAb and TPOAb with allergic diseases.

	B	SD	Wald	Degrees of freedom	*P* value	Exp (B)	95% confidence interval	
Sex	0.423	0.337	1.576	1	.209	1.526	0.789	2.953
Age	−0.011	0.015	0.559	1	.455	0.989	0.960	1.018
Prevalence of hypertension	0.017	0.461	0.001	1	.971	1.017	0.412	2.512
Prevalence of diabetes	0.472	0.664	0.506	1	.477	1.603	0.437	5.888
TPOAb positive	0.256	0.352	0.527	1	.468	1.291	0.647	2.577
TgAb positive	−0.975	0.341	8.187	1	.004	0.377	0.193	0.735

SD = standard deviation, TgAb = thyroglobulin antibody, TPOAb = thyroid peroxidase antibody.

identified thyroid autoantibodies TgAb or TPOAb as potential risk factors for AR, AD, or CSU in Chinese patients. This phenomenon can be explained by the formation of immune complexes in AITD patients by autoantibodies and thyroid antigens, such as TPO. These antigen-antibody complexes can further bind to the Fc receptor on mast cells, basophils, or other immune cells to induce the activation of allergy responses in the skin or mucosa.[30,31] An alternative explanation is a genetic predisposition to allergies and autoimmune diseases that leads to the development of hypersensitivity reactions. For example, concurrent AITD with type 1 diabetes has been shown to occur more commonly in patients who express the human leukocyte antigen DR3, indicating the potential involvement of certain genetic factors in the association between AITD and allergy disorders.[32]

Our study demonstrated for the first time that elevated TgAb and TPOAb can significantly increase the risk of allergic diseases using clinical data from China. However, some limitations of this study should be acknowledged. First, this was a single-center retrospective study with a small sample size. In addition, we did not analyze the time course and relationships between the levels of thyroid autoantibodies and allergic diseases. Second, we could not identify the roles of TgAb and TPOAb in the pathogenesis of atopic immune reactions in this study. Further studies are necessary to clarify these points.

5. Conclusions

In conclusion, thyroid autoantibodies, especially TgAb, have a notable impact on allergic disorders. Although TA is not common, thyroid autoantibodies may be involved in the pathogenesis of other atopic reactions, including AR, AD, and CSU. Therefore, screening for thyroid function and autoimmunity is clinically useful to monitor the clinical progress of patients with allergic symptoms.

Author Contributions

Conceptualization: CZ, XL, LW, and YL.
Data curation: CZ, YL, and WS.
Formal analysis: CZ, YL, and WS.
Funding acquisition: CZ and YL.
Investigation: CZ, XL, and YL.
Methodology: CZ, XL, LW, and YL.
Project administration: CZ and XL.
Resources: CZ and YL.
Software: CH, XL, and LW.
Supervision: XL, LW, KX, ZT, and YL.
Validation: CH, XL, and LW.
Visualization: CZ, XL, and LW.
Writing-original draft: CZ, XL, and LW.
Writing-review and editing: XL, LW, KX, ZT, and YL.
All authors read and approved the final articles.

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