

The risk of autoimmune connective tissue diseases in patients with atopy: A nationwide population-based cohort study

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ABSTRACT

Background: The relationship between autoimmune connective tissue disease (ACTD) and atopy is controversial.

Objectives: To investigate the risks of ACTDs in patients with atopic triad diseases, including atopic dermatitis, allergic rhinitis, and asthma, by using a nationwide data base.

Methods: A cohort of 155,311 patients newly diagnosed with atopic dermatitis, allergic rhinitis, or asthma in 2002–2011 was obtained from the Taiwan National Health Insurance Research Database. An age- and sex-matched control group was selected from the same data base. The association between atopy and ACTD was investigated by using Cox proportional hazards regression analyses.

Results: Atopic dermatitis, allergic rhinitis, and asthma were present in 12.1, 78.6, and 26.3%, respectively, of the patients with atopy. The presence of atopic diseases increased the overall risk of ACTDs (incidence rate ratio 1.85 [95% confidence interval {CI}, 1.52–2.25]). The hazard ratio (HR) for ACTDs remained higher after adjusting for age, sex, urbanization level, socioeconomic status, and comorbidities. Individual risks of systemic lupus erythematosus (HR 1.58 [95% CI, 1.06–2.37]), rheumatoid arthritis (HR 1.74 [95% CI, 1.31–2.33]), and Sjögren syndrome (HR 2.49 [95% CI, 1.71–3.63]) were also higher. The coexistence of atopic triad diseases increased the risk of ACTDs from 1.80 (95% CI, 1.48–2.21) for one atopic disease to 3.29 (95% CI, 1.22–8.88) for three atopic diseases.

Conclusion: The presence of atopic triad diseases is significantly associated with risks of systemic lupus erythematosus, rheumatoid arthritis, and Sjögren syndrome, and their coexistence exacerbates this risk. To our knowledge, this was the first study that reported an increased risk of Sjögren syndrome among patients with atopy.

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Atopic dermatitis (AD), allergic rhinitis (AR), and asthma comprise the atopic triad and usually arise in early childhood. The overall 8-year prevalences of AD, AR, and asthma in Taiwan are 6.7, 26.3, and 11.9%, respectively, and it is firmly established that AD often coexists with AR and asthma.¹ Major pathogenetic features of atopic diseases are raised levels of immunoglobulin E and a characteristic T-helper type 2 (Th2) cell cytokine pattern.^{2,3} The relationship between the occurrence of Th2-mediated allergic diseases and Th1-mediated autoimmune conditions is

controversial and has been discussed in various epidemiologic studies.^{4,5} A shift toward Th2 immune responses might protect against the development of Th1-mediated diseases.^{6,7} However, previous reports indicate autoantibodies positivity in allergic disease^{8–10} and show the coexistence of Th2 and Th1 diseases.¹¹ Because T-helper cells are involved in the pathogenesis of both atopic disorders and autoimmune diseases, a positive association between them has been speculated.

In recent years, epidemiologic studies established that both systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA) are associated with atopic diseases.^{12–16} These observational studies had a case-control design^{12,13} or retrospective cohort design with age restriction.^{14–16} Possible associations between atopy and other autoimmune connective tissue diseases (ACTD), such as systemic sclerosis (SSc), dermatomyositis (DM) and polymyositis (PM), or Sjögren syndrome (SS) have not been verified. We, therefore, conducted a nationwide population-based cohort study that included a large number of patients with atopy to investigate the association between atopic diseases and subsequent risks of ACTDs.

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METHODS

Data Source

This study was conducted based on the data processed by the National Health Insurance Research Database and subsequently released by the National Health Research Institute (NHRI). Taiwan launched a single-payer National Health Insurance program in 1995 to finance the nationwide health care for all residents. There currently are >23 million enrollees, which represent ~99.6% of the Taiwan population as of the end of 2015.¹⁷ We obtained Longitudinal Health Insurance Database 2000 from the NHRI. This data base consists of scrambled identification codes, personal information, and medical records of a randomly selected sample of one million National Health Insurance beneficiaries, which represented ~5% of the enrolled subjects in 2000. The age and sex distributions correspond to those of the registry of beneficiaries. For the protection of privacy, the identities of the patients, physicians, and institutions were scrambled in accordance with the data regulations of the National Health Insurance Administration, Ministry of Health and Welfare, Taiwan. This study was conducted in accordance with the Helsinki Declaration and was evaluated and approved by the institutional review board of Taipei Veterans General Hospital (2016-05-011CC).

Identification of Atopic Disease

For this retrospective cohort study, we selected patients diagnosed with any of the atopic triad diseases, including AD, AR and asthma, from January 1, 2002, to December 31, 2011. These patients were identified according to the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM): ICD-9-CM code 691.X for AD, ICD-9-CM code 477.X for AR, and ICD-9-CM code 493.X for asthma. The patients had to have been diagnosed with at least one disease of the atopic triad. We included subjects diagnosed with these diseases at least three times according to outpatient clinic records or at least once during hospitalization. To include only incident cases of atopic diseases, those with atopic diseases diagnosed before 2002 were excluded. The date of the first diagnosis was taken as the index date for each patient. Those with a diagnosis of autoimmune disease established before the diagnosis of atopic disease were excluded. A total of 155,311 patients with atopic diseases were included in this study.

Control Group

One-to-one nonatopic comparison controls were selected from the same data base by matching the atopic cohort by sex, age, and index date. All the control subjects with a diagnosis of ACTD before their index

date were excluded. The comparison group included 155,311 subjects.

Outcome Variable

We followed up each subject to identify patients who received catastrophic illness certificates for ACTDs by their associated ICD-9-CM codes. Issuance of a catastrophic illness certificate to patients with major ACTDs requires comprehensive laboratory and clinical assessment, and a full board review by rheumatologists commissioned by the Bureau of National Health Insurance. The insured who fulfill one of these definite diagnoses can be exempted from medical copayments. The investigated ACTDs in this study included SLE (ICD-9-CM code 701.0), SSc (ICD-9-CM code 710.1), RA (ICD-9-CM codes 714.0, 714.1, 714.2, 714.3, 714.4), DM/PM (ICD-9-CM codes 710.3, 710.4), and SS (ICD-9-CM code 710.2).

Covariates

To investigate the role of urbanization, all 365 townships of Taiwan were stratified into three levels (urban, suburban, and rural) according to the standards established by the NHRI based on a cluster analysis of the 2000 Taiwan census data. Socioeconomic status was classified based on monthly income as low (<New Taiwan dollars [NT] \$20,000 [U.S. \$667]), medium (NT \$20,000–39,999 [U.S. \$667–1334]), or high (NT ≥\$40,000 [U.S. ≥\$1334]). We also identified relevant comorbidities, including hypertension (ICD-9-CM codes 401.X–405.X), diabetes mellitus (ICD-9-CM code 250.X), hyperlipidemia (ICD-9-CM code 272.X), renal disease (ICD-9-CM codes 580.X–589.X), chronic liver disease and cirrhosis (ICD-9-CM code 571.X), and cancer (ICD-9-CM codes 140.X–208.X) for both the case and control cohorts.

Statistical Analysis

The demographic information of patients with and without atopic disease was compared by using a χ^2 test for categorical variables. After adjusting for age, sex, urbanization level, socioeconomic status, and comorbidities as potential confounders, Cox proportional-hazards analysis was used to investigate the risk of developing ACTDs in both cohorts. A two-sided *p* value of <0.05 was considered to represent a statistically significant difference. All data processing and statistical analyses were performed with Stata 12 (Stata Corp., College Station, TX) and SAS 9.1 (SAS System for Windows; SAS Institute, Cary, NC).

RESULTS

Characteristics of Patients with Atopy and Control Subjects

Of the 155,311 patients newly diagnosed with atopic diseases, 73,585 were male and 81,726 were female

Table 1 Baseline characteristics of study cohorts

Variables	Atopy Cohort (n = 155,311)	Control Cohort (n = 155,311)	p
Atopic dermatitis, no. (%)	18,759 (12.1)		
Allergic rhinitis, no. (%)	122,068 (78.6)		
Asthma, no. (%)	40,805 (26.3)		
Age, mean $\pm$ SD, y	36.5 $\pm$ 22.2	36.3 $\pm$ 22.3	0.999
Age, no. (%)			
<18 y	38,540 (24.8)	38,540 (24.8)	0.999
18–39 y	50,622 (32.6)	50,622 (32.6)	
40–49 y	20,928 (13.5)	20,928 (13.5)	
50–59 y	17,704 (11.4)	17,704 (11.4)	
60–69 y	12,633 (8.1)	12,633 (8.1)	
≥ 70 y	14,884 (9.6)	14,884 (9.6)	
Sex, no. (%)			
Male	73,585 (47.4)	73,585 (47.4)	0.999
Female	81,726 (52.6)	81,726 (52.6)	
Socioeconomic status, no. (%)			
Low	79,064 (50.9)	85,104 (54.8)	<0.001
Medium	45,197 (29.1)	43,679 (28.1)	
High	31,050 (20)	26,528 (17.1)	
Urbanization level, no. (%)			
Urban	95,017 (61.2)	93,560 (60.2)	<0.001
Suburban	46,906 (30.2)	47,503 (30.6)	
Rural	13,388 (8.6)	14,247 (9.2)	
Comorbidities, no. (%)			
Hypertension	28,579 (18.4)	21,244 (13.7)	<0.001
Diabetes mellitus	11,713 (7.5)	9323 (6)	<0.001
Hyperlipidemia	17,922 (11.5)	11,816 (7.6)	<0.001
Renal diseases	4918 (3.2)	3296 (2.1)	<0.001
Chronic liver diseases and cirrhosis	16,432 (10.6)	10,366 (6.7)	<0.001
Cancer	4109 (2.7)	3022 (2)	<0.001

SD = Standard deviation.

patients, with a mean $\pm$ standard deviation age of 36.5 $\pm$ 22.2 years. AD, AR, and asthma were present in 12.1, 78.6, and 26.3%, respectively, of our atopic patients. The prevalences of hypertension, diabetes, hyperlipidemia, renal diseases, liver diseases, and cancer were higher among the patients with atopy (all $p < 0.001$) (Table 1).

Risk of Autoimmune Connective Tissue Diseases among Patients with Atopy

Overall, 456 patients (292 in the case cohort and 164 in the control cohort) were diagnosed with ACTDs during the follow-up. Compared with the control group, the overall incidence rate ratio (IRR) for ACTDs was 1.85-fold (95% confidence interval [CI], 1.52- to 2.25-fold) higher among the patients with atopy. Moreover, individual IRRs of SLE (IRR 1.53 [95% CI, 1.01–2.35]), RA (IRR, 1.71 [95% CI, 1.27–2.30]), and SS (IRR 2.50 [95% CI, 1.71–3.74]) were significantly higher among the patients with atopy (Table 2).

Hazard Ratios of Autoimmune Connective Tissue Diseases among Patients with Atopy

After adjusting for age, sex, urbanization level, socioeconomic status, and comorbidities, the hazard ratio (HR) for risk of ACTDs was 1.87-fold (95% CI, 1.54- to 2.26-fold) higher among the patients with atopy. The association of atopic diseases and ACTDs exhibited a dose-response relationship, being strongest among those with all three diseases of the atopic triad (HR 3.29 [95% CI, 1.22–8.88]), moderate among those with two diseases of the atopic triad (HR 2.13 [95% CI, 1.56–2.90]), and mild in those with only one disease of the atopic triad (HR 1.80 [95% CI, 1.48–2.21]). The HRs for ACTDs increased with age (HR 1.03 [95% CI, 1.03–1.04]) and were lower among the men (HR 0.26 [95% CI, 0.21–0.33]) (Table 3).

We further evaluated the risks of individual ACTDs among the patients with atopy (Table 4). The HRs for risks of SLE, RA, and SS were 1.58-fold (95% CI, 1.06- to 2.37-fold), 1.74-fold (95% CI, 1.31- to 2.33-fold), and

Table 2 Crude IRRs in atopy and control cohorts

Variables	Atopy Cohort (950,568 person-years)	Control Cohort (987,468 person-years)	IRR (95% CI)
Total autoimmune connective tissue diseases			
Total no.	292	164	
Incidence rate*	30.7	16.6	1.85 (1.52–2.25)
Systemic lupus erythematosus			
Total no.	59	40	
Incidence rate*	6.2	4.1	1.53 (1.01–2.35)
Systemic sclerosis			
Total no.	5	3	
Incidence rate*	0.5	0.3	1.73 (0.34–11.15)
Rheumatoid arthritis			
Total no.	125	76	
Incidence rate*	13.2	7.7	1.71 (1.27–2.30)
Dermatomyositis and/or polymyositis			
Total no.	9	6	
Incidence rate*	0.9	0.6	1.56 (0.50–5.32)
Sjögren syndrome			
Total no.	94	39	
Incidence rate*	9.9	4	2.50 (1.71–3.74)

IRR = Incidence rate ratio. CI = confidence interval.

*Per 100,000 person-years.

Table 3 HRs of autoimmune connective tissue diseases in the atopy cohort

Variables	Model 1, HR (95% CI)	Model 2, HR (95% CI)
No. atopic triad diseases		
Any no.	1.87 (1.54–2.26)	
One		1.80 (1.48–2.21)
Two		2.13 (1.56–2.90)
Three		3.29 (1.22–8.88)
Age	1.03 (1.03–1.04)	1.03 (1.03–1.04)
Sex		
Female	1	1
Male	0.26 (0.21–0.33)	0.26 (0.21–0.33)
Socioeconomic status		
Low	1	1
Medium	1.10 (0.88–1.38)	1.11 (0.88–1.39)
High	1.15 (0.89–1.49)	1.15 (0.90–1.49)
Urbanization level		
Urban	1	1
Suburban	1.12 (0.91–1.38)	1.12 (0.91–1.38)
Rural	1.13 (0.82–1.56)	1.13 (0.82–1.56)
Comorbidities		
Hypertension	0.57 (0.44–0.75)	0.57 (0.43–0.75)
Diabetes mellitus	0.88 (0.62–1.25)	0.88 (0.62–1.25)
Hyperlipidemia	1.01 (0.75–1.36)	1.01 (0.75–1.36)
Renal diseases	1.22 (0.77–1.94)	1.22 (0.77–1.94)
Chronic liver diseases and cirrhosis	1.54 (1.18–2.02)	1.54 (1.18–2.01)
Cancer	1.22 (0.75–1.96)	1.21 (0.75–1.96)

HR = Hazard ratio; CI = confidence interval.

Table 4 HRs for individual autoimmune connective tissue diseases in the atopy cohort

Variables	Atopy, HR (95% CI)	One Atopic Triad Disease, HR (95% CI)	Two or Three Atopic Triad Diseases, HR (95% CI)
Systemic lupus erythematosus	1.58 (1.06–2.37)	1.48 (0.97–2.26)	2.11 (1.13–3.96)
Systemic sclerosis	1.68 (0.40–7.15)	1.62 (0.36–7.32)	2.02 (0.21–19.70)
Rheumatoid arthritis	1.74 (1.31–2.33)	1.69 (1.25–2.28)	2.03 (1.29–3.20)
Dermatomyositis and/or polymyositis	1.49 (0.53–4.24)	1.20 (0.38–3.76)	2.97 (0.73–12.02)
Sjögren syndrome	2.49 (1.71–3.63)	2.50 (1.70–3.68)	2.45 (1.36–4.39)

HR = Hazard ratio; CI = confidence interval.

2.49-fold (95% CI, 1.71- to 3.63-fold) higher, respectively, in patients with atopy than in the controls. A similar dose-response relationship between diseases of the atopic triad and individual ACTD was found. Thus, compared with the control group, the HRs for SLE (HR 2.11 [95% CI, 1.13–3.97]), RA (HR 2.03 [95% CI, 1.29–3.20]), and SS (HR 2.45 [95% CI, 1.36–4.39]) were significantly higher among those with two or three diseases of the atopic triad.

DISCUSSION

This was a large-scale population-based cohort study that investigated the relationship between incident atopic diseases and the risk of subsequent ACTDs. Given the relatively low incidence of ACTDs, a large sample size was critical to achieve a sufficient statistical power. The obtained incidence rates per 100,000 person-years of SLE, SSc, RA, DM/PM, and SS were 4.1–6.2, 0.3–0.5, 7.7–13.2, 0.6–0.9, and 4–9.9, respectively and were compatible with values from previous reports.^{18–20} Patients with atopy were at a 1.87-fold higher overall risk of developing ACTDs, with a dose-response relationship observed when an increasing number of atopic triad diseases were present. Individual ACTDs, such as SLE, RA, and SS, were significantly associated with atopic diseases.

A growing body of evidence accumulated in recent decades indicates that atopic diseases can be accompanied by a variety of comorbidities, such as obesity, metabolic syndrome, gastroenteritis, nephritic or nephrotic syndrome, psychiatric diseases, and site-specific cancers.^{2,21,22} Our results also confirmed higher prevalences of hypertension, diabetes, hyperlipidemia, renal diseases, liver diseases, and cancer among patients with atopy in comparison with the general population. Although the exact pathophysiologic mechanisms are not yet fully understood, the concept on atopy as a multiorgan systemic disease is widely accepted. Our findings confirmed a link between SLE and atopic diseases indicated in recent epidemiologic studies.^{12,13,16} Similar immune dysfunctions and overproduction of cytokines and inflammatory mediators are present in SLE and atopic diseases, which possibly

account for the increased risk of SLE in patients with atopy.²³

RA is a disease with strong Th1 polarization. Early studies support an inverse association between RA and atopy.^{6,7,24} For example, atopy was decreased in patients with RA, and RA severity was reduced in patients with both diseases.⁷ However, the corresponding studies were small and probably underpowered. In a recent large-scale German population-based cohort study, patients ages ≤40 years with prevalent AD were at a significantly greater risk of developing RA than patients without AD.¹⁵ Another epidemiologic study, conducted in Taiwan, also showed that asthma and AR were significantly associated with incident RA in patients ages ≥20 years.¹⁴ When combined with the results of the present study, these findings challenge the validity of the long-standing Th1/Th2 paradigm, which suggests a far more complex mechanism underlying the association between autoimmune and allergic diseases. Furthermore, we discovered a 2.5-fold increased risk of subsequent SS among patients with atopy. To the best of our knowledge, such an association was not previously shown. An increased risk of developing asthma in patients with SS obtained in another population-based cohort study is in accordance with this result.²⁵

The present study also revealed a trend toward an increased risk of SSc and DM/PM in patients with atopy, although without statistical significance. This may be a consequence of the relatively low incidence of SSc and DM/PM. Further large-scale studies may be warranted to investigate the association. The parallel appearance of allergic and autoimmune conditions in some patients may indicate that such aberrations of the immune system have a common pathophysiologic mechanism. The presence of autoantibodies in some allergic conditions suggests an autoimmune basis for these conditions.^{8–10} Immunoglobulin E has been suggested to play a central role in the pathogenesis of inflammatory autoimmune disorders.²⁶ The new paradigm identifies additional lymphocyte subsets, such as Th17 and regulatory T cell, and novel soluble factors.^{27–30} A relatively newly discovered group of mol-

ecules, the T-cell immunoglobulin and mucin domain gene family, has also been shown to be involved in allergy and autoimmunity.³¹ Epigenetic changes secondary to prolonged systemic inflammation might be another mechanism that involves autoimmunity.^{32,33} The above findings help to explain experimental observations not predicted by the Th1/Th2 paradigm and provide a new model for interpreting the interaction of autoimmune and allergic diseases.

CONCLUSION

In this study, the presence of ACTDs was correlated with the number of atopic diseases, female sex, and age. Even though information on the severity of the disorders was unavailable, the link between the number of atopic triad diseases and an increased risk of ACTDs might indicate that the risk of ACTDs increases with more serious or uncontrolled chronic inflammation related to atopy. A higher risk of ACTDs in women is not surprising, given that they are generally more susceptible to autoimmunity. Sex hormones, genes encoded in the sex chromosomes, and sex-specific behaviors likely contribute to the difference.³⁴ Also, it has been reported that age is a risk factor for ACTDs.^{13,14,16} Because most ACTDs do not develop until the third or fourth decade of life, accumulation of epigenetic changes with aging may provide the impetus for the onset of disease in susceptible individuals.³³ However, the underlying pathophysiology needs further study.

The results of this research should be viewed in the light of several limitations. First, administrative data were subject to possible coding errors. The patients with atopy may have been misclassified. However, such nondifferential misclassification of some patients would lead to an underestimation of the observed effects, which would result in more conservative conclusions. Second, this study might have a lack of information on the severity of diseases. Third, there might be ascertainment bias, with patients with an index diagnosis more likely to be diagnosed with another disease than patients without an index diagnosis. This bias could lead to an increase in the rate of diagnosis of ACTDs among patients with atopy. However, the chance of such misdiagnosis is likely minimal because of the mandatory medical insurance and good accessibility of medical care in Taiwan.

A major strength of our study was its nationwide population-based setting, with a relatively large number of patients with atopy and 10 years of follow-up that facilitated proper evaluation of the associations between atopy and ACTDs. Our findings provided solid epidemiologic evidence that atopy was a risk factor for ACTDs, including SLE, RA, and SS, with the increased risk of SS demonstrated for the first time.

Furthermore, the coexistence of atopic triad diseases elevated the risks of developing ACTDs. Therefore, patients with atopy should be monitored more carefully for signs of autoimmune disorders.

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