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Abstract

A previous study, with relatively small number of patients, showed that prior *Mycobacterium tuberculosis* (TB) may precipitate SLE in patients from endemic areas. The purpose of the study was to investigate the relationship between prior TB infection and systemic lupus erythematosus (SLE) from the National Health Insurance Research Database (NHIRD) in Taiwan. Cases of SLE and TB were identified from the NHIRD with corresponding ICD-9 codes 710.0 and 011-018, respectively, from January 2000 to December 2008. A total of 2,721 cases of SLE and 10,823 control subjects were included in data analysis. The average annual incidence rate was 8.1 per 100,000. The annual incidence rates of SLE decreased from 6.38 per 100,000 to 2.55 per 100,000 during 2000–2008. Compared with the control subjects, SLE patients were more likely to be white collar workers ($P = 0.0005$), reside in highly urbanized areas ($P = 0.0140$), and have higher incomes ($P = 0.0088$). TB was much more prevalent in SLE patients than in the control subjects (1.8 vs. 0.9%, $P < 0.001$). The mean time interval between diagnosis of TB and SLE was 45.58 ± 39.0 months. On multivariate analysis, TB was the greatest potential risk factor for precipitating SLE (OR = 2.11, 95% CI = 1.49–3.00). In addition, patients with co-existing TB and DM had a higher risk of SLE than the control group (OR = 3.91, 95% CI 1.84–8.31). In conclusion, this study suggests that there is an increased risk of precipitating SLE among patients with TB in Taiwan from a nationwide health insurance research dataset. Mycobacterial infections could trigger autoimmune diseases in experimental studies. Furthermore, a study with relatively small number of patients revealed that prior TB may precipitate SLE in patients from endemic

	areas. There is an increased risk of precipitating SLE among patients with TB in Taiwan from a nationwide health insurance research dataset during a 9-year period.
Keywords (separated by '-')	Systemic lupus erythematosus - Tuberculosis - Risk factor - Health insurance
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ORIGINAL ARTICLE

Tuberculosis as a risk factor for systemic lupus erythematosus: results of a nationwide study in Taiwan

Yu-Chao Lin · Shinn-Jye Liang · Yi-Heng Liu · Wu-Huei Hsu · Chuen-Ming Shih · Fung-Chang Sung · Wei Chen

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Abstract A previous study, with relatively small number of patients, showed that prior *Mycobacterium tuberculosis* (TB) may precipitate SLE in patients from endemic areas. The purpose of the study was to investigate the relationship between prior TB infection and systemic lupus erythematosus (SLE) from the National Health Insurance Research Database (NHIRD) in Taiwan. Cases of SLE and TB were identified from the NHIRD with corresponding ICD-9 codes 710.0 and 011-018, respectively, from January 2000 to December 2008. A total of 2,721 cases of SLE and 10,823 control subjects were included in data analysis. The average annual incidence rate was 8.1 per 100,000. The annual incidence rates of SLE decreased from 6.38 per 100,000 to 2.55 per 100,000 during 2000–2008. Compared with the control subjects, SLE patients were more likely to be white collar workers ($P = 0.0005$), reside in highly urbanized areas ($P = 0.0140$), and have higher incomes ($P = 0.0088$). TB was much more prevalent in SLE patients than in the control subjects (1.8 vs. 0.9%, $P < 0.001$). The mean time interval between diagnosis of TB and SLE was 45.58 ± 39.0 months. On multivariate analysis, TB was the greatest potential risk factor for precipitating SLE (OR = 2.11, 95% CI = 1.49–3.00). In addition, patients with co-existing TB and DM had a higher risk of SLE than the control group (OR = 3.91, 95% CI 1.84–8.31). In conclusion, this study suggests that there is an increased risk of precipitating SLE among patients with TB in Taiwan from a nationwide health insurance research dataset. Mycobacterial infections could trigger autoimmune diseases in experimental studies. Furthermore, a study with relatively small number of patients revealed that prior TB may precipitate SLE in patients from endemic areas. There is an increased risk of precipitating SLE among patients with TB in Taiwan from a nationwide health insurance research dataset during a 9-year period.

Keywords Systemic lupus erythematosus · Tuberculosis · Risk factor · Health insurance

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Introduction

Systemic lupus erythematosus (SLE), an autoimmune disease with multiple organ involvement, is a highly

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pleiomorphic disease predominantly affecting young women of reproductive age [1]. The pathogenesis of SLE is still unclear, but it may be related to several factors, such as hormones, genetics, environment and virus infection [2]. The hall mark of this disorder is the presence of autoantibodies to single stranded and double stranded DNA. *Mycobacterial tuberculosis* (TB) infection is still a major health problem worldwide, both in developed [3] and developing countries [4, 5]. It affects almost one-third of the global population and is the secondary cause of death among infectious diseases [6, 7]. Experimental models of autoimmune diseases such as mycobacteria-induced arthritis have shown many features of autoimmunity [8, 9], and monoclonal antibodies raised against TB can cross react with DNA [10]. Thus, it is possible that mycobacterial infections could trigger autoimmune diseases.

Several studies have shown an increased prevalence of tuberculosis in SLE patients, both from non-endemic and endemic countries [11, 12]. Treatment for SLE leading to immunosuppression may be the cause of the high prevalence of TB. However, there are only limited studies on whether TB infection precipitates SLE. Kanjaksha et al. [13] reported that TB plays a role in precipitating SLE in genetically predisposed patients. However, their sample size was relatively small.

TB infection is a common disease in Taiwan, with an incidence of 74.6 cases per 100,000 population [14]. Taiwan initiated a National Health Insurance program in 1995, and the data available from this program offer a unique opportunity for research. In the present study, we used a 9-year nationwide population-based dataset to determine the risk of SLE among patients with TB.

Methods and materials

Data source

Insurance claim data were obtained from the National Health Research Institute in Taiwan (NHRI) with the authorization of the Bureau of National Health Insurance, Department of Health. The universal National Health Insurance (NHI) program was implemented in Taiwan in 1995. It covers approximately 99% of the total 23 million population and includes contracts with 97% of hospitals and clinics in Taiwan. The National Health Research Institute established and updates the NHI Research Database, which contains all claims data from 1996 to 2008. From this research database, a dataset was created by randomly selecting 1 million insured subjects, including information on ambulatory care, inpatient care, dental service, prescription drugs, medical institution, physician providing the services and the registration file. Personal identification is encrypted before the release of the dataset for public access. We used this random dataset in this study with approval from the National Health Research Institute.

Criteria and definitions

In this population-based nested case–control study, we identified patients aged more than 18 years with newly diagnosed systemic lupus erythematosus (SLE, International Classification of Disease Diagnoses, Ninth revision [ICD-9-CM] code 710.0) from outpatient claim files or hospitalization records during 2000–2008. Control subjects were aged more than 18 years and were randomly selected from individuals in the database without SLE at a ratio of 1:4 (patients vs. controls) during the same time period. In Taiwan, the diagnosis of SLE was confirmed based on the fulfilling of American College of Rheumatology criteria. In addition, in our strict policy, SLE is included in the list of catastrophic illnesses published by the Department of Health, Executive Yuan. The approval of the status of catastrophic illness is subject to evaluation and review by the Bureau of NHI, and patients with catastrophic illness certificates are eligible for exemption from insurance premiums and co-payments. Therefore, catastrophic illness patient data are highly accurate and reliable. Under this verification, a total of 2,721 cases of SLE and 10,823 control subjects were included in the data analysis.

TB and comorbidities

Study subjects were considered to have history of tuberculosis infection (TB) if they had received medical care at least twice, including outpatient visits and/or hospitalizations, for a principal diagnosis of TB (ICD-9-CM code 011-018) prior to the diagnosis of SLE. In Taiwan, TB diagnosis was confirmed by microbiological analysis and/or histopathological evaluation. The comorbidities identified in this study were diabetes mellitus (DM, ICD-9-CM code 250), end stage renal disease (ESRD, ICD-9-CM code 585) and liver cirrhosis (ICD-9-CM codes 571.2 and 571.5). To estimate the levels of urbanization where the study subjects registered for NHI, we calculated the population density (persons/km^2) for each of the 319 townships and city districts in Taiwan. The areas with population densities in the first quartile and fourth quartile were classified as areas of low urbanization and high urbanization, respectively. Areas in the remaining two quartiles were categorized as moderate urbanization.

Statistical analysis

We calculated the annual incidence rates of SLE as the numbers of SLE cases divided by population. The temporal

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trend in the occurrence of SLE was examined using the Poisson regression model. We compared the differences in age, sex, occupation, level of urbanization, residential area and monthly income between cases with SLE and control subjects using the Chi-square test. To assess the association between TB and the risk of new occurrence of SLE, we performed multiple logistic regression analyses to estimate odds ratios (ORs) and 95% confidence intervals (CIs) of SLE associated with TB after controlling for age, gender, occupation, levels of urbanization and income. The regression analyses were repeated in patient subgroups stratified by status of DM. All analyses were performed using SAS statistical software (version 9.1 for Windows; SAS Institute, Inc., Cary, NC). The results were considered to be statistically significant when two-tailed *P* values were less than 0.05.

Results

A total of 2,721 cases of SLE and 10,823 control subjects were included in the data analysis. Among the 2,721 SLE cases, 49 patients (1.8%) were diagnosed with antecedent TB.

The annual incidence rates of SLE over the 9-year period are shown in Table 1. The incidence rates of SLE decreased from 6.38 per 100,000 to 2.55 per 100,000 during 2000–2008. Using Poisson regression models, the trends of SLE incidence significantly decreased with increasing year ($P < 0.001$). Compared with the control subjects, SLE patients were more likely to be white collar workers ($P = 0.0005$), reside in highly urbanized areas ($P = 0.0140$), and have higher incomes ($P = 0.0088$) (Table 2). TB was much more prevalent in SLE patients than in the control subjects (1.8 vs. 0.9%, $P < 0.001$). However, SLE patients tended to have a higher prevalence rate of DM (8.5 vs. 9.9%, $P = 0.023$).

Table 1 Annual incidence of systemic lupus erythematosus in Taiwan during 2000–2008

Year	Total population	*n*	Incidence (rate/per 100,000 persons)
2000	954,021	609	6.38
2001	941,337	429	4.56
2002	928,760	373	4.02
2003	918,043	306	3.33
2004	909,689	292	3.21
2005	902,561	291	3.22
2006	894,806	237	2.65
2007	886,904	270	3.04
2008	877,959	224	2.55

Systemic lupus erythematosus = icd9 237 code: 710.0

Table 2 Sociodemographic characteristics and comorbidities of cases with systemic lupus erythematosus and control subjects

	Control subjects (*N* = 10,823) *n* (%)	Patients with SLE (*N* = 2,721) *n* (%)	*P* value
Gender			0.8919
Women	8,771 (81.0)	2,202 (80.9)	
Men	2,052 (19.0)	519 (19.1)	
Age (years)			0.4363
18–44	6,534 (60.4)	1,606 (59.0)	
45–64	3,029 (28.0)	789 (29.0)	
≥65	1,260 (11.6)	326 (12.0)	
Occupation			0.0005
White collar	5,979 (55.2)	1,572 (57.8)	
Blue collar	3,481 (32.2)	772 (28.4)	
Others	1,363 (12.6)	377 (13.8)	
Urbanization			0.0140
Low	381 (3.5)	72 (2.6)	
Moderate	2,932 (27.1)	696 (25.6)	
High	7,510 (69.4)	1,952 (71.8)	
Monthly income (NTD)			0.0088
<15,000	4,078 (37.7)	1,024 (37.6)	
15,000–29,999	5,309 (49.0)	1,277 (46.9)	
≥30,000	1,436 (13.3)	420 (15.5)	
TB			<0.0001
No	10,729 (99.1)	2,672 (98.2)	
Yes	94 (0.9)	49 (1.8)	
DM			0.0226
No	9,748 (90.1)	2,490 (91.5)	
Yes	1,075 (9.9)	231 (8.5)	
ESRD			0.5714
No	10,779 (99.6)	2,712 (99.7)	
Yes	44 (0.4)	9 (0.3)	
Liver cirrhosis			0.1778
No	10,816 (99.9)	2,717 (99.8)	
Yes	7 (0.1)	4 (0.2)	

NTD new Taiwan dollar, *TB* tuberculosis, *DM* diabetes mellitus, *ESRD* end stage renal disease

Compared with the control subjects, TB patients had a crude OR of 2.09 for SLE (95% CI = 1.48–2.97) (Table 3). The strength of the association between TB and SLE was at the same level after controlling for other potential risk factors (OR = 2.11, 95% CI = 1.49–3.00, model 1). The mean time interval between diagnosis of TB and SLE was 45.58 ± 39.0 months.

Table 4 presents the association between TB and risk of SLE among patients with and without DM. TB patients were at a higher risk of SLE than the control subjects in the

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Table 3 Odds ratios and 95% confidence intervals of systemic lupus erythematosus in relation to tuberculosis infection and other potential risk factors

	Unadjusted	Adjusted[a]
	OR (95% CI)	OR (95% CI)
Gender		
Women	1.00 (reference)	1.00 (reference)
Men	1.01 (0.91–1.12)	0.98 (0.88–1.09)
Age (years)		
18–44	1.00 (reference)	1.00 (reference)
45–64	1.06 (0.96–1.17)	1.08 (0.98–1.19)
≥65	1.05 (0.92–1.20)	1.09 (0.95–1.25)
Occupation		
White collar	1.00 (reference)	1.00 (reference)
Blue collar	0.84 (0.77–0.93)	0.87 (0.78–0.97)
Others	1.05 (0.93–1.20)	1.11 (0.96–1.28)
Urbanization		
Low	1.00 (reference)	1.00 (reference)
Moderate	1.26 (0.96–1.64)	1.26 (0.96–1.64)
High	1.38 (1.06–1.78)	1.33 (1.03–1.73)
Monthly income (NTD)		
<15,000	1.00 (reference)	1.00 (reference)
15,000–29,999	0.96 (0.87–1.05)	1.03 (0.93–1.15)
≥30,000	1.17 (1.02–1.33)	1.18 (1.02–1.36)
Tuberculosis infection		
No	1.00 (reference)	1.00 (reference)
Yes	2.09 (1.48–2.97)	2.11 (1.49–3.00)

NTD new Taiwan dollar

[a] Adjusted for all variables listed in table

Table 4 Adjusted odd ratios for systemic lupus erythematosus in relation to tuberculosis infection by status of diabetes

	Diabetes	
	No (N = 12,238)	Yes (N = 1,306)
	OR (95% CI)	OR (95% CI)
Tuberculosis infection		
No	1.00 (reference)	1.00 (reference)
Yes	1.76 (1.18–2.65)	3.91 (1.84–8.31)

OR odds ratio, *CI* confidence interval

Models were adjusted for gender, age, occupation, levels of urbanization, and monthly income

non-DM group (adjusted OR = 1.76, 95% CI = 1.18–2.65). The association was stronger in the DM group (OR = 3.91, 95% CI = 1.84–8.31).

Discussion

This is the first nationwide population-based study evaluating the relationship between TB and SLE in Taiwan. In this study, there was a significantly higher incidence of preceding TB infection among SLE patients (1.8%) than in the general population (0.9%, $P < 0.0001$). On multivariate analysis, TB was the greatest potential risk factor for precipitating SLE (OR = 2.11, 95% CI = 1.49–3.00). We suggest, therefore, that prior TB infection may play a role in precipitating SLE in an endemic area.

The incidence rate of SLE varies from country to country. Naleway et al. [15] showed that the age-adjusted incidence rate of SLE was 5.1 per 100,000 in the USA, and Nightingale et al. [16] revealed that the nationwide incidence rate was 3.0 per 100,000 in the UK. However, there are scant recent data on the incidence rates of SLE in adult populations in Asia. Iseki et al. [17] demonstrated that the crude incidence of SLE in Okinawa from 1972 to 1991 was 0.9 to 2.9 per 100,000 by hospital and clinical-based studies. In the present study, the incidence rate of SLE was around 3–6 per 100,000 from 2000 to 2008. The incidence decreased steadily during the study period from 6.38 per 100,000 in 2000 to 2.55 per 100,000 in 2000, which is consistent with a previous report [18]. The trend of a declining incidence of SLE in Taiwan might be related to the health insurance system offered by the government since 1995. The health insurance system has increased the number of patients seeking medical care, hence the incidence increased steadily from 1999 to 2002 [19]. Thereafter, the incidence rate steadily declined reaching a plateau in the last 6 years. However, whether the decline in the incidence of SLE is a real effect or an effect of health policy needs further investigation.

Case ascertainment in the present study was according to clinical coding, which may raise the question of diagnostic accuracy. However, the criteria we used for SLE recruitment has been accepted by several journals [18–20]. In addition, diagnosis of TB is quite strict in Taiwan. Once TB has been diagnosed using ICD-9 code 011-018, either in outpatient clinics or hospitals, the Center for Disease Control monitors the patient carefully and regularly.

From the previous study, 20% of SLE patients were found to have confirmed antecedent tuberculosis over 2-year period. However, in our study, there were only 1.8% of SLE patients were found to have prior TB infection. It is probably because that the prevalence of tuberculosis is higher in India than in Taiwan. The prevalence of tuberculosis in India is 505 per 100,000, and it is 113 per 100,000 in Taiwan.

Interestingly, we also observed that TB patients were at a higher risk of SLE than the control subjects in the non-DM group (adjusted OR = 1.76, 95% CI = 1.18–2.65). The association was even stronger in the DM group (OR = 3.91, 95% CI = 1.84–8.31). Whether this relationship truly exists, an explanation of the mechanism will need further investigations.

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Regarding the relationship between TB infection and autoimmunity, several phenomena have been addressed. First, several autoantibodies can be detected in TB patients, such as antinuclear antibody [21] and rheumatoid factor [22]. In addition, anti-TB drugs, such as isoniazid, can induce autoantibodies and SLE-like syndrome [23, 24]. Second, "molecular mimicry" prevents the autoantibodies from the mycobacteria reacting with mycobacteria, and causes them to react with host antigen. Shoenfeld et al. [25] showed that monoclonal anti-TB antibodies were found to react with ssDNA, dsDNA and anti-DNA autoantibodies from SLE patients binding the glycolipids of part of the mycobacterial cell wall. Third, the clinical expression of autoimmune diseases may be modified by permissive and protective environmental factors. One study demonstrated that TNF polymorphism plays an opposite role of autoimmunity and tuberculosis in a northwestern Colombian population [26]. Taken together, the above findings suggest that tuberculosis could be one of the factors that triggers autoimmunity.

In conclusion, this is the first nationwide population-based study evaluating the relationship between TB and SLE in Taiwan. We suggest that prior TB infection may play a role in precipitating SLE in an endemic area.

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Conflict of interest None of the authors have any potential conflicts of interest.

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