Chinese Lupus Treatment and Research group (CSTAR) registry: X. family history in relation to lupus clinical and immunological manifestations

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Abstract

Objective

This study aimed to examine the associations between family history and clinical manifestations and immunologic characteristics of lupus in China.

Methods

Based on their family history, lupus patients from the Chinese Lupus Treatment and Research group (CSTAR) registry were categorised: familial lupus (FL), family history of other rheumatic disorders (RD), and sporadic lupus (SL). Demographic data, clinical manifestations, and laboratory data were compared among these three groups.

Results

A total of 2,104 patients from CSTAR were included, with 34 (1.6%) in the FL group, 50 (2.4%) in the RD group, and 2,020 (96.0%) in the SL group. There were no significant differences in age or gender among these groups (p=0.36 and p=0.75, respectively). The prevalence of discoid rash and positivity of anti-RNP antibodies differed significantly among the three groups. Photosensitivity and neurological disorder were marginally significantly different among the three groups (p=0.05). No statistical differences were observed in other clinical manifestations or laboratory results. In the FL group, first-degree relatives (25/34, 73.5%) had higher susceptibility to lupus. Rheumatoid arthritis (RA) (35/50, 70.0%) was the most frequent non-lupus rheumatic disorder in the RD group.

Conclusion

Among lupus patients, the rate of familial lupus was lower in Chinese patients than among other ethnicities. Familial lupus cases are found mainly among their first-degree relatives. A family history of lupus did not significantly affect clinical phenotypes, except for higher frequency of discoid rash and anti-RNP in the FL group, and more anti-RNP positivity in the RD group.

Key words

lupus, family history, CSTAR, phenotypes

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Introduction

Systemic lupus erythematosus (SLE) is a chronic inflammatory disease of unknown aetiology that can affect almost any organ system, accompanied by heterogeneous clinical manifestations and immunologic characteristics. The complexity of the aetiology and pathogenesis in SLE and its genetic and environmental factors are great challenges to both clinicians and researchers. Strong indications of a genetic component in SLE come from studies in families as well as in monozygotic and dizygotic twins, which identified several SLE-associated loci and genes (*e.g.* IRF5, PTPN22, CTLA4, STAT4 and BANK1) (1-7). However, the severity and outcome of familial lupus were not found to be significantly different from those of sporadic cases among different ethnicities except in juvenile SLE, with a greater severity of disease in the highly consanguineous Kuwaiti and Sultanate of Oman population (8-13). It remains unknown whether the clinical manifestations and immunologic characteristics of familial lupus differ from those of sporadic lupus in the Chinese population.

To examine whether family history is associated with differences in clinical and laboratory phenotypes among Chinese patients with SLE, we analysed associations between familial history and clinical/laboratory manifestations based on data from the Chinese SLE Treatment and Research group (CSTAR) registry.

Materials and methods

Patient enrolment

Our analysis was based on data from the CSTAR registry, which was the first nationwide online registry of Chinese patients with SLE, launched in April 2009.The database depicted the clinical characteristics of patients with lupus from 104 rheumatology centres, covering 30 provinces in China. To ensure the quality of data collection, all sites were trained and assessed using the same standard operating procedures (SOPs) and protocol (14-16). Treating rheumatologists took patients' family history and medical history. Coordinators were in charge of enrolling patients, and physicians inspected the data randomly. All patients met SLE classification criteria as revised by the American College of Rheumatology (ACR) in 1997 (17).

The study was approved by the central ethics committee of Peking Union Medical College Hospital, which was the leading site for CSTAR (review number no. S-478). Other centres also obtained ethics approval if required by local regulations. Written informed consent was obtained from all patients.

Family history and degree of relationship

Familial lupus (FL) patients were defined as those who had at least one other family member (specifically, a first-, second- or third-degree relative) with confirmed diagnosis of SLE. Sporadic lupus (SL) patients were those who had no familial history of lupus or other rheumatic disorder. Patients with a family history of other rheumatic disorders other than lupus made up the other rheumatic disorder (RD) group.

The degree of relationship describes the proportion of genes shared by two blood relatives. The above definition of first-, second-, or third-degree relatives comes from the UK NHS National Genetics and Genomics Education Centre (www.geneticseducation.nhs.uk/genetic-glossary/181-first-degree-relative).

Clinical data collection

Typical systemic manifestations were assessed and entered in the system: rash, oral ulceration, fever, vasculitis, arthritis, myositis, lupus nephritis, pleuritis, pericarditis, and neuropsychiatric disorders. The SLE Disease Activity Index (SLEDAI) at the time of enrolment in the registry was calculated.

Sample collection and analysis

Blood samples were collected in the ward during hospitalisation or on-site visit to an out-patient department during follow-up, and tested at local laboratories. All laboratories were in compliance with the "Regulations of clinical laboratories in medical institutions" from the China Food and Drug Administration (CFDA). Autoantibody spectrum included anti-nuclear antibody (ANA), anti-extractable nuclear

antigen (ENA) antibody panel, anti-double-stranded (ds) DNA, and anti-phospholipid (APL) antibody. ANA and anti-dsDNA antibody were detected mainly by immunofluorescence assay with the Hep-2 cell line. The Anti-ENA antibody panel (including anti-Sm, anti-SSA, anti-SSB, anti-RNP, and anti-rRNP antibodies) was tested by immunoblotting. APL antibody was tested by enzyme-linked immune-sorbent assay (anticardiolipin and anti-β2 glucoprotein I antibody) and/or dilute Russell viper venom test (lupus anticoagulant). Routine laboratory findings were recorded, including leucopenia, thrombocytopenia, hypocomplementaemia, and proteinuria. The methods were authenticated by Chinese health authorities.

Statistical analysis

Demographic data are presented as mean values (SD). Distribution of clinical phenotype and positivity of autoantibodies in different groups are expressed as patient number and percentage. The distributions of the categorical and continuous variables across the three groups were assessed with Mantel-Haenszel Chi-square test and analysis of variance (ANOVA) wherever appropriate. All tests of significance were two sided, and a *p*-value of <0.05 was considered to be statistically significant. Statistical analysis was performed using SPSS 17.0.

Results

Demographic characteristics of three groups of lupus patients

There were 2,104 patients with lupus registered in CSTAR up to February 2010. The overall proportion of males to females was 10.1% with similar distribution among the three groups. The age at diagnosis was 27.2±11.0 yrs in the FL group, 31.3±10.7 yrs in the SL group, and 30.4±12.4 yrs in the RD group A history of familial lupus or other rheumatic disorders did not change the age at diagnosis as it did not reach significant differences among the groups (p=0.31; Table I).

Family history

Of 2,104 patients, 34 (1.6%) were found to have familial history of lupus (FL group); 50 (2.4%) were identified as having familial history of another rheumatic disorder (RD group). However, the vast majority of patients (2,020, 96.0%) were confirmed as sporadic lupus cases (SL group).

Among the 34-member in FL group, 25 (73.5%) cases involved first-degree relatives, 5 involved second-degree relatives, and 4 third-degree relatives. Furthermore, 5 FL patients had more than two cases of SLE in their families, 4 of which involved first-degree relatives; one family had involvement of both first- and second-degree relatives. In the 50-member group with familial members who had other rheumatic disorders, the most common disorder was rheumatoid arthritis (35 cases), followed by Sjögren's syndrome (6), ankylosing spondylitis (3), undifferentiated connective tissue disease (3), and one case each of dermatomyositis, mixed connective tissue disease, and progressive systemic sclerosis. Additionally, 37 (74.0%) of the 50 cases involved first-degree relatives, 4 (8.0%) second-degree relatives, and 9 (18.0%) third-degree relatives.

Table I. Demographic data of FL, RD and SL groups.

	FL (n=34)	RD (n=50)	SL (n=2020)	*p*-value
Gender				0.67
Female	31 (91.2)	47 (94.0)	1836 (90.9)	
Male	3 (8.8)	3 (6.0)	184 (9.1)	
Age on diagnosis	27.2 (11.0)	31.3 (10.7)	30.4 (12.4)	0.31

FL: familial lupus; RD: lupus with family history of other rheumatic disorder; SL: sporadic lupus. The differences across the three groups were assessed with ANOVA. *p*-value <0.05 was considered to be statistically significant.

Table II. Clinical phenotype among three groups of lupus patients.

		FL (n=34)	RD (n=50)	SL (n=2020)	*p*-value
Malar rash					0.83
	No	14 (41.2)	32 (64.0)	1049 (51.9)	
	Yes	20 (58.8)	18 (36.0)	971 (48.1)	
Discoid rash					0.01
	No	29 (85.3)	45 (90.0)	1912 (94.7)	
	Yes	5 (14.7)	5 (10.0)	108 (5.3)	
Photosensitivity					0.05
	No	22 (64.7)	33 (66.0)	1523 (75.4)	
	Yes	12 (35.3)	17 (34.0)	497 (24.6)	
Oral ulcers					0.74
	No	27 (79.4)	36 (72.0)	1575 (78)	
	Yes	7 (20.6)	14 (28.0)	445 (22)	
Non-erosive arthritis				0.69	
	No	18 (52.9)	15 (30.0)	924 (45.7)	
	Yes	16 (47.1)	35 (70.0)	1096 (54.3)	
Serositis					0.79
	No	31 (91.2)	38 (76.0)	1690 (83.7)	
	Yes	3 (8.8)	12 (24.0)	330 (16.3)	
Renal disorder					0.76
	No	18 (52.9)	24 (48.0)	1064 (52.7)	
	Yes	16 (47.1)	26 (52.0)	956 (47.3)	
Neurological disorder				0.05	
	No	34 (100.0)	50 (100.0)	1919 (95.0)	
	Yes	0 (0)	0 (0)	101 (5.0)	
Haematological disorder				0.91	
	No	14 (41.2)	23 (46.0)	886 (43.9)	
	Yes	20 (58.8)	27 (54.0)	1134 (56.1)	
SLEDAI		9.1 ± 7.1	9.7 ± 7.1	9.7 ± 6.8	0.87

FL: familial lupus; RD: lupus with family history of other rheumatic disorder; SL: sporadic lupus. The distributions of clinical phenotype across the three groups were assessed with Mantel-Haenszel Chi-square test. *p*-value <0.05 was considered statistically significant.

Table III. Laboratory features of three groups of lupus patients.

		FL (n=34)	RD (n=50)	SL (n=2020)	*p*-value
ANA					0.22
	No	0 (0)	0 (0)	40 (2)	
	Yes	34 (100)	50 (100)	1980 (98)	
Anti-Sm					0.90
	No	29 (85.3)	41 (82)	1684 (83.4)	
	Yes	5 (14.7)	9 (18)	336 (16.6)	
Anti-RNP					0.01
	No	29 (85.3)	40 (80)	1846 (91.4)	
	Yes	5 (14.7)	10 (20)	174 (8.6)	
Anti-SSA					0.87
	No	26 (76.5)	39 (78)	1541 (76.3)	
	Yes	8 (23.5)	11 (22)	479 (23.7)	
Anti-SSB					0.92
	No	32 (94.1)	41 (82)	1807 (89.5)	
	Yes	2 (5.9)	9 (18)	213 (10.5)	
Anti-rRNP					0.31
	No	11 (73.3)	13 (59.1)	736 (75.3)	
	Yes	4 (26.7)	9 (40.9)	242 (24.7)	
APL					0.79
	No	8 (47.1)	14 (63.6)	501 (55.8)	
	Yes	9 (52.9)	8 (36.4)	397 (44.2)	
Anti-dsDNA					0.95
	No	26 (76.5)	32 (64)	1433 (70.9)	
	Yes	8 (23.5)	18 (36)	587 (29.1)	

FL: familial lupus; RD: lupus with family history of other rheumatic disorder; SL: sporadic lupus. The distributions of laboratory test results across the three groups were assessed with Mantel-Haenszel Chi-square test. *p*-value <0.05 was considered statistically significant.

Clinical phenotype among three groups of lupus patients

All clinical characteristics, including initial symptom, affected organ system, and SLEDAI at enrolment visit, are shown in Table II.

In the FL group, 14.7% (5 of 34) patients of experienced discoid rash, which was significantly higher than the 5.3% (108 out of 2,020) in the SL group and the 10.0% (5 of 50) in the RD group (p=0.01). The positivity for photosensitivity showed a marginally significant declining tendency from FL to RD to SL: 35.3% *vs*. 34.0% *vs*. 24.6%, respectively (p=0.05). It is very interesting that neurological disorders were present only in the SL group (5%), a marginally significant statistical difference (p=0.05). The prevalence of non-erosive arthritis was 47.1% in the FL group, much lower than the 54.3% in the SL group and the 70.0% in the RD group. However, the difference did not reach statistical significance. The prevalence other clinical manifestations, such as malar rash, oral ulcers, serositis, renal disorders, and haematological disorders, were comparable among the three groups, and SLEDAIs were comparable at enrolment.

Prevalence of auto-antibodies among three groups of lupus patients

Among the antibodies tested, the distribution of anti-RNP was significantly different: it was much lower in SL (8.6%) than in FL (14.7%) or RD (20.0%) groups (p=0.01). The proportion of positive ANA was 98.0% in SL and 100% in the FL and RD groups; there was no significant difference in ANA positivity among the groups (Table III). As a specific marker for lupus, levels of anti-Sm antibody did not differ significantly among the groups; anti-SSA and anti-SSB were also comparable, as were distributions of anti-rRNP and APL. Anti-dsDNA, which is considered a marker for disease activity, was not significantly different among the three groups, which was consistent with the results of SLEDAI. These results confirm the absence of significant differences in disease activity among the groups.

Discussion

The fact that lupus is a heterogeneous disease whose pathogenesis remains unclear has severely hindered innovations in treatment. Accurate characterisation of the disease will greatly improve our understanding of lupus, its public health burden, and implications for health-care planning. Efforts have been made to identify and collect data from more lupus (18-21). Specifically, CSTAR has made efforts to characterise Chinese patients with lupus. The more than 2,000 registered lupus cases in this analysis allow the creation of more precise and meaningful subgroup analyses to improve our understanding of the disease.

Among lupus patients, the proportion of familial lupus was 1.6% in our registry, similar to a recent population-based family study (1.3%) from Taiwan (22). However, it was much lower than in previous western studies (5.0%–9.4%) (8-10). In studies from the Middle East, the prevalence of familial lupus was far higher, with 27.4% in Kuwaiti patients and 36% with juvenile lupus in the Sultanate of Oman (8, 13). More interestingly, the prevalence of familial lupus was also low (2.3%) in other Chinese studies of patients with lupus nephritis (22). Of familial lupus cases, 70.6% involved first-degree relatives in this study, which was similar to previous studies, including one from Taiwan (22). However, more first-degree relative cases involved parent/offspring than siblings in our study (10, 11, 23).

The reason for the relatively low prevalence of familial lupus in our Chinese population with lupus is unclear. Possible reasons included genetic heterogeneity from ethnic origin, highly consanguineous gathering of local inhabitant, and incomplete coverage of the registry, though the data in this study covers almost all the provinces in China. Future studies would improve our understanding of these differences by implementing diligent analysis of lupus heterogeneities pedigrees and genome analysis (24-26).

Given the considerable evidence for genetic susceptibility to lupus, the familial lupus patients with increased genetic risk might raise earlier onset of lupus and make diagnosis of lupus earlier, comparing to other two groups (2, 27-29). However, the mean ages at diagnosis in the FL group did not differ significantly from those in the RD and SL groups in our study. On the other hand, it is consistent with previous ob-

Table IV. Comparison of clinical characteristics between familial and sporadic lupus (familial/sporadic lupus).

Author, year (ref.)	Geographical area	Total number of patients (FL, %)	Sex ratio (% of female, (*p*-value)	Mean age of diagnosis (*p*-value)	Fever (%, *p*-value)	Malar rash (%, *p*-value)	Photosensitivity (%, *p*-value)	Discoid rash (%, *p*-value)	Oral ulcers (%, *p*-value)	Arthritis (%, *p*-value)
Michel, 2001 (10)	France	137 (11, 8%)	92/93 (NS)			51/50 (NS)	52/51 (NS)	27.7/15 (0.034)	4.4/15 (0.01)	80/72 (NS)
Koskenmies, 2001 (9)	Finland	1200 (113, 9.4%)[b]	90.3/90.3 (NA)[b]	34.9/34.3 (NS)[b]		46/50 (NS)	69/64 (NS)	5/12 (NS)	17/12 (NS)	79/88 (NS)
Zhang, 2009 (21)	China	1461 (34, 2.3%)[g]	88.2/88.2 (NS)	28.8/30.2 (NS)	58.8/26.5 (NS)	50.0/52.0 (NS)	14.7/13.7 (NS)	0/1 (NS)	11.8/11.8 (NS)	73.5/51.0 (NS)
Burgos, 2010 (8)	US	644 (32, 5.0%)	90/90 (NS)						78.1/60.3 (0.04)	
Our study	China	2104 (34, 1.6%)	91.2/90.9 (NS)	27.2/30.4 (NS)		58.8/48.1 (NS)	35.3/24.6 (0.05)	14.7/5.3 (0.01)	20.6/22.0 (NS)	47.1/54.3 (NS)

Author, year (ref.)	Geographical area	Pericarditis (%, *p*-value)	Serositis (%, *p*-value)	Renal disorder (%, *p*-value)	Neurologic Disorder (%, *p*-value)	Raynaud phenomenon (%, *p*-value)	Associated APS (%, *p*-value)	Haematologic disorders (%, *p*-value)	ANA (%, *p*-value)	Anti-dsDNA (%, *p*-value)
Michel, 2001 (10)	France		31.1/28 (NS)	21.1/36 (0.03)	3.3/11 (NS)	35.5/41 (NS)	14.4/26 (NS)	27.7/38[a] (NS)	92/92 (NS)	73.3/77 (NS)
Koskenmies, 2001 (9)	Finland	10/20 (0.04)	15/25 (NS)[c]	27/29 (NS)	11/7 (NS)[d]		13/7 (NS)[e]	87/91 (NS)[f]	98/98 (NS)	70/83 (0.02)
Zhang, 2009 (21)	China		20.6/29.4 (NS)[h]	100/100	14.7/8.8 (NS)			82.4/74.5 (NS)[i]	97.1/98.9 (NS)	45.5/61.3 (NS)
Burgos, 2010 (8)	US				12.5/3.8 (0.04)					
Our study	China		8.8/16.3 (NS)	47.1/47.3 (NS)	0/5.0 (0.05)			58.8/56.1 (NS)	100/98.0 (NS)	23.5/29.1 (NS)

The ratio in table was familial cases/sporadic cases.
a: haematologic disorder included thrombocytopenia and haemolytic anaemia. **b**: Controls matched for sex, age, and duration of SLE symptoms. **c**: pleuritis in Finland group. **d**: Neurologic disorders included convulsion cases and psychosis cases in the Finland group. **e**: Only deep venous thrombosis cases were associated with APS in the Finland group. **f**: Haematologic disorders included leukopenia and thrombocytopenia. **g**: All cases in this group were SLE with lupus nephritis. **h**: Serositis included serositis, pleuritic, and pericarditis. i: Haematologic disorders included haemolytic anaemia, leukopenia, and thrombocytopenia.

servations that development of lupus is a dose-dependent combination of environmental exposures, estrogenic hormones, and genetic predisposition (30). Discoid rash was significantly more common in our FL group than in the other two groups. Photosensitivity marginally significantly declined from FL to RD to SL groups, in parallel to decreasing in genetic predisposition. On the other hand, although neurological involvements were only observed in the SL group which almost indicated the neurological involvements were exempted from familial aggregation of lupus and other rheumatic disorders, more works are required to prove it. We did not find differences in imbalanced impairment in other organs/systems among the three groups.

We compared the clinical and laboratory features of familial and sporadic lupus from other cohorts and summarised the results in Table V. Compared to our Chinese cohort, there were more oral ulcer cases in familial lupus in the French and US cohorts. Furthermore, more pericarditis cases were associated with sporadic lupus in the Finnish cohort and more renal disorder cases in the French cohort. More interestingly, there were more neurologic disorders associated with familial lupus in the US cohort, which is the opposite observation of our study. In terms of laboratory, more anti-dsDNA positivity was seen in sporadic lupus in the Finnish cohort, compared with our cohort (10). In general, the overall clinical profile of our three groups, including clinical manifestations and serologic tests, was consistent with other studies, despite some slight differences in clinical manifestations (9-11, 23). The reason for such differences will hopefully be clarified by emerging large-scale genomic analyses.

Accumulating data suggest that genome-wide association studies (GWAS) have been successful in identifying many new susceptibility loci for lupus, providing strong motivation for novel immunological work (30). Furthermore, regression analyses have been performed to link disease susceptibility loci to specific genes affecting disease manifestations (26, 27, 31). GWAS on our patient population is under preparation, and those results will provide more precise information on the relevance of genetic factors and clinical features.

Within the lupus auto-antibody panel, the positivity of anti-RNP was significantly lower in the sporadic lupus group than in the FL and RD groups. Except for anti-RNP, there was no significant difference in other auto-antibody tests. In another study of lupus nephritis patients from China measuring ANA, anti-dsDNA, anti-Sm, Anti-RNP, anti-SSA/B, and APL, there was no difference between familial lupus and sporadic lupus (23).

In terms of disease activity, SLEDAI, including anti-dsDNA, was collected. Given that anti-dsDNA and SLEDAI are dynamic parameters of lupus activity and fluctuate with treatment, comparing SLEDAI from different stages among the three groups did not add value to the study.

In conclusion, the rate of familial lupus was lower in our lupus population, and was associated mainly with first-degree relatives. Familial history was not significantly associated with clinical phenotypes of lupus, except for a higher rate of discoid rash and anti-RNP in familial lupus (both *p*-values were 0.05). As with data from other countries, our findings also support the hypothesis that familial SLE and non-familial SLE are the same clinical entity; although the lupus phenotype may be influenced by ethnic origin (32-34). GWAS data will soon reveal more precision information on the relevance of genetic factors and clinical features in our patient population.

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