Clinical characteristics of 1020 childhood-onset systemic lupus erythematosus: data from a health centre in China

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Abstract

Objective

Childhood-onset systemic lupus erythematosus (cSLE) is a multisystem autoimmune disease characterised and presents partially differently from adults. A large cSLE cohort study is lacking in China. The present study aimed to determine the clinical characteristics in a large population of patients with cSLE, and compare with adult-onset SLE (aSLE) in an SLE cohort of China.

Methods

The retrospective study included patients with cSLE diagnosed at the Beijing Children's hospital between July 2006 and October 2020. All patients met at least 4 of ACR classification criteria for SLE. In addition, data including demographic, clinical and serologic data were collected. Our data were compared with other cSLE cohorts and Chinese aSLE cohorts.

Results

A total of 1020 patients were included in this study, comprising 808 female and 212 male patients (female to male ratio, 3.8:1). The mean age at diagnosis of lupus was 11.1 years (range 1.0–17.2). It took on average 6 months (range 0.1–132) from first symptoms to cSLE diagnosis and over 12 months in 12% of patients. The most common primary manifestations at onset were rash (37.2%), fever (33.4%), nephropathy (14.2%) and arthritis (13.6%). The most common clinical manifestations were rash (67.9%) and fever (57.5%). 59.4% of patients had haematological involvement, 46.0% had lupus nephritis, 33.2% had arthritis. cSLE was more active and associated with more inflammation than aSLE patients.

Conclusion

This study is a large single-centre study on cSLE from China and clarifies the clinical phenotype and autoantibody spectrum of cSLE. The clinical manifestations and autoantibody spectrum of cSLE are diverse, with regional and populational differences.

Key words

systemic lupus erythematosus, children, clinical characteristics

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Introduction

Systemic lupus erythematosus (SLE) is a complex, multifactorial disease of unknown aetiology in which significant immunological abnormalities have been identified (1). Although the peak age of onset occurs in the middle younger (16–50 years), approximately 15–20% of patients are children or adolescents under 16 years (2, 3). Clinical presentation and organ involvement in childhood-onset systemic lupus erythematosus (cSLE) are largely heterogeneous (2). In China, most of the studies of cSLE reported to date have been limited by the relatively small sample sizes. There has been no large cohort study in cSLE examining the clinical presentation, laboratory features, and autoantibody profile.

Clinical characteristics, underlying pathomechanisms, disease progression, and outcomes vary between age groups (4). According to previous studies, cSLE patients have more frequent involvement in the renal, haematological, and central nervous systems and less arthritis and pulmonary involvement than adult-onset SLE (aSLE) patients (5-7). The clinical and laboratory phenotypes of cSLE were reported by the GLADEL Cohort, UK cSLE Cohort *et al*. (8, 9). In addition, the demographic, clinical and laboratory features of cSLE vary in different ethnic groups (10).

In the present study, we aimed to determine the frequency and characteristics of the clinical signs, symptoms, laboratory features in a large population of patients with cSLE and to compare clinical and immunological manifestations with cSLE in other regions and aSLE in Chinese SLE Treatment and Research group (CSTAR), an SLE cohort of China (11).

Methods

Patients

This study is a retrospective cohort including 1020 patients with cSLE diagnosed at the age of 18 or younger at the Beijing Children's hospital, China, between July 2006 and October 2020. All patients met at least 4 of the American College of Rheumatology (ACR) classification criteria for SLE (12). The study's protocol was approved by the Research Ethics Board of Beijing Children's Hospital, Capital Medical University, China.

Clinical data

Clinical and immunologic criteria were defined based on Systemic Lupus International Collaborating Clinics Classification Criteria for Systemic Lupus Erythematosus (SLICC) (13). Demographic data included age at diagnosis, time interval to diagnosis (interval between first signs/symptoms to cSLE diagnosis), family history of rheumatic diseases, and gender. Initial manifestations meant the manifestations present before the first visit to a doctor. SLE Disease Activity Index 2000 (SLEDAI-2K) was used to score the disease activity (14). Lupus nephritis histopathology at diagnosis was analysed according to the World Health Organisation classification scheme (15). We searched PUbMED for large cohort studies on cSLE and Chinese adult lupus cohort studies, and then extracted data for comparison with our cohort. Low complement refers to C3 below 0.89g/ml or C4 below 0.15g/ml. Thrombocytopenia refers to platelets below 100x 10^9/L. Leukopenia means that the white blood cells fall below 4 x 10^9/L.

Autoantibody detections

The presence of autoantibodies, including antinuclear antibody (ANA), anti-dsDNA, anti-Sm, anti-SSA, anti-SSB, anti-RNP, and anti-Ro52 *et al*. were measured. ANA was detected using immunofluorescence with Hep-2 cell line, anti-dsDNA was detected using immunoblotting or indirect immunofluorescence and anti-ENA was detected using immunoblotting. Antiphospholipid antibodies (aPL), including lupus anticoagulant (LA), anticardiolipin (aCL) IgG and ACL IgM, and anti-β2 glycoprotein I (IgG, IgM, and IgA) were detected in most patients. LA was detected using two methods: diluted Russell's viper venom time (DVRRT) and silica clotting time (SCT).

Statistical analyses

Continuous variables were expressed as mean±standard deviation (SD) when presenting normal distribution or me-

dians (interquartile ranges) for skewed distributions, while categorical variables were presented as numbers (n) and percentages. Chi-square and Fisher's exact tests were used to compare categorical data. Statistical analyses were performed using SPSS version 19.0 software (SPSS Inc., Chicago, IL, USA), and p-values<0.05 were considered significant.

Results

Demographics

A total of 1020 Chinese patients were included in this study, comprising 808 (79.2%) female and 212 (20.8%) male patients (female to male ratio, 3.8:1). Sixty-six percent of the children were diagnosed for the first time with SLE. In addition, 34% of children were diagnosed in other hospital. The mean age at diagnosis of lupus was 11.1 years (range 1.0–17.2). It took an average of 6 months (range 0.1–132) from first symptoms to cSLE diagnosis and more than 12 months in 12% of patients. There were no significant differences in the age at diagnosis or the delay of diagnosis between genders.

Forty-four (4.3%) of 1020 patients had a family history of immune diseases, including 12 with SLE, 13 cases of rheumatoid arthritis, 6 cases of psoriasis, 4 cases of Henoch-Schonlein purpura, 2 cases of ankylosing spondylitis, 2 cases of immune thrombocytopenic purpura, 1 case of IgA nephropathy, 1 case of Crohn's disease, 1 case of Wegener's granulomatosis, 1 case of undifferentiated connective tissue disease, and 1 case of sclerosis.

Clinical manifestations

The most common manifestations at onset were rash (379, 37.2%), fever (341, 33.4%), nephropathy (145, 14.2%), arthritis (139, 13.6%), and haematocytopenia (100, 12.7%). As shown in Table I, the clinical manifestations of patients before diagnosis of systemic lupus erythematosus in Beijing Children's hospital were diverse, in which 693 (67.9%) patients presented malar rash, 606 (59.4%) patients had haematological involvement, 586 (57.5%) had a fever, 46.0% had lupus nephritis, 340 (33.3%) had arthritis, 265 (26%) had thrombocytopenia, 203 (19.9%) had oedema, and 167 (16.4%) presented oral ulcers. Six percent patients were diagnosed with secondary Sjögren's syndrome and 2.8% patients presented macrophage activation syndrome (MAS). Ninety-two children underwent renal biopsy, 4 cases (4.3%) were class I, 6 cases (6.5%) were class II, 27 cases (29.3%) were class III, 30 cases (32.6%) were class IV, 6 cases (6.5%) were class V, 6 cases (6.5%) were class III+V, 13 (14.1%) were classified as class IV+V.

Table I. Manifestation of cSLE patients.

Manifestations	Total	percent
Malar rash	693	67.9%
Fever	586	57.5%
Arthritis	339	33.2%
Thrombocytopenia	265	26.0%
Oedema	203	19.9%
Oral ulcers	167	16.4%
Proteinuria	143	14.0%
Swollen lymph nodes	115	11.3%
Haematuria	109	10.7%
Photosensitivity	106	10.4%
Alopecia	82	8.0%
Fatigue	73	7.2%
Parotid gland enlargement	68	6.7%
Discoid rash	50	4.9%
Convulsions	47	4.6%
Headache	38	3.7%
Ecchymosis	36	3.5%
Epistaxis	26	2.5%
Oliguria	24	2.4%
Pancreatitis	18	1.8%
Diffuse thyroid damage	18	1.8
Chest pain	14	1.4%
Raynaud phenomenon	13	1.3%
Dizziness	10	1.0%
Coma	6	0.6%
Submandibular gland involvement	6	0.6%
Dry mouth	5	0.5%
Hypertension	5	0.5%
Chest tightness	5	0.5%
Muscle weakness	4	0.4%
Lethargy	4	0.4%
Dry eyes	4	0.4%
Muscle ache	2	0.2%
Difficulty breathing	2	0.2%
Irritability	2	0.2%
Limb pain	2	0.2%
Livedo reticularis	1	0.1%
Haemoptysis	1	0.1%
Gangrene	1	0.1%
Emotional abnormalities	1	0.1%
Bleeding gums	1	0.1%
Extended menstrual period	1	0.1%

Laboratory features

The median white blood cell counts, median platelet counts and median haemoglobin were 4.8 (3.4–7.4) x 10^9/L, 177 (115–257) x 10^9/L and 109 (94–123) g/L, respectively. The median levels of C reactive protein and ESR were 4 (1–7) mg/L and 23 (10–47) mm/h.

The autoantibodies profile included the presence of ANA in 1020 (100%) of the cases, anti-dsDNA in 625 (61.3%), anti-Sm in 219 (21.5%), and anti-SSA in 414(40.5%). Other detected autoantibodies and their frequencies are shown in Figure 1. APL was tested in 819 patients and was positive in 510 (62.3%). However, only 29 (2.8%) of the patients in the cohort were diagnosed with antiphospholipid antibody syndrome (APS) base on 2006 revised antiphospholipid syndrome classification criteria (16). The aPL profile is shown in Figure 2. Additionally, complement C3 decreased in 89.3% patients, C4 in 84.7% patients, C3 or C4 decreased in 92.5% patients, and both C3 and C4 were reduced in 81.2% of the patients.

SLE disease activity

SLEDAI scores were performed when the patients were admitted to the hospital. Results revealed that 149 (14.6%) cases belong to a stable group (<5), 398 (39%) belong to a mild active group (5-9), 314 (30.8%) fit into a moderate active group (10-14), and 159 (15.6%) cases belong to a severe active group (>14).

Clinical features of patients with different SLE onset ages and geographical areas

The demographic, clinical, and laboratory features of SLE are variable in different ethnic groups and different onset ages. We compared our data with CSTAR, an adult cohort in China, and with cohorts of children in different geographical regions. The results are presented in Table II.

Discussion

Systemic lupus erythematosus is a common rheumatic disease in children. At present, there are reports on the clinical and serological characteristics of SLE in many regions, but there is still a lack of research on large-scale systemic lupus erythematosus regard-

Fig. 1. Positive rates of different ENAs at the onset of diagnosis.

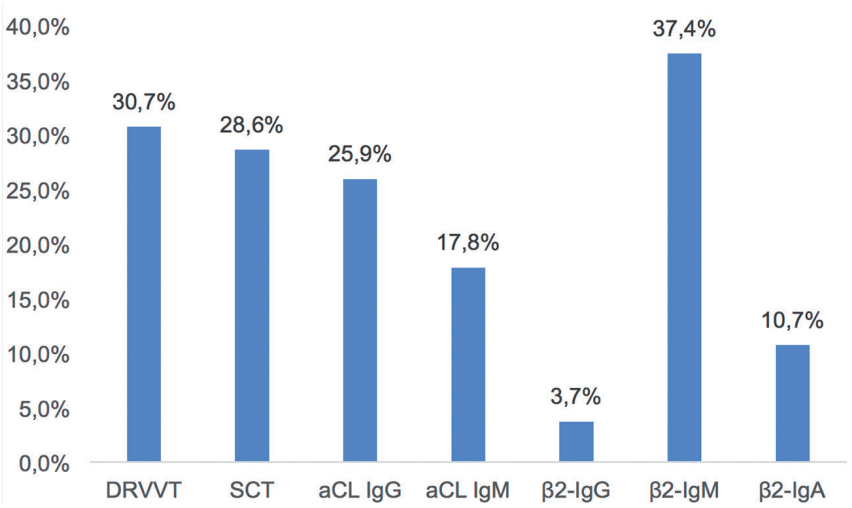

Fig. 2. Positive rates of different aPL at the onset of diagnosis.

ing Chinese children. This study reported the immunologic, serologic and clinical phenotypes of 1020 cases of cSLE. Although this is a single-centre study, our patients are from more than 30 provinces and cities in China and 34% of patients are referred to our hospital from other hospitals. In addition, we also reviewed and compared clinical and immunological manifestations with aSLE in CSTAR and cSLE in other regions, suggesting that the clinical characteristics of SLE are different between populations and regions.

Consensus regarding the cut-off age for defining cSLE is still missing in the literature. In our study, 18 years was considered the upper limit of the definition of cSLE. However, some studies consider 16 years as the threshold. Such variations may contribute to different results across studies (3, 20).

Early diagnosis and treatment of cSLE affect the prognosis of children with lupus. Fiorot *et al*. (10) reported that the average time from symptom to diagnosis was 3 months. Moreover, the GLADEL cohort (9) reported that this time in Latin America was 4 months. However, our data revealed that it took an average of 6 months from symptom to diagnosis, and 12% of children needed 1 year to be diagnosed. Our data suggests that we still need a significant improvement in the early diagnosis of lupus.

The clinical manifestations of cSLE are diverse and highly heterogeneous. We found more than 40 clinical manifestations in our study, the most common of which are fever, rash, arthritis, and thrombocytopenia. In addition, there are some rare manifestations, such as livedo reticularis, emotional abnormalities, and bleeding gums. This study comprehensively describes the clinical manifestations of cSLE, which will improve paediatricians' ability to recognise cSLE and perform the early diagnosis of cSLE.

SLE is a diverse disease varying by the age of onset (21). Our study's most common initial symptoms were rash, fever, neuropathy, arthritis, and haemocytopenia. Compared to adults (11), except for the fever, the proportion of initial symptoms of cSLE was significantly lower. It shows that the onset of SLE in children is not typical, and the early diagnosis is more complex, which may be one of the reasons for the delayed diagnosis.

It has been suggested that cSLE has a more severe disease course than adult SLE. Our study shows that acute inflammatory reactions, such as fever and rash, were significantly more frequent compared to adults, and the proportion of nervous system damage and activity (SLEDAI >5) was significantly higher than that in adults. In addition, many studies found a higher prevalence of anti-dsDNA, anti-RNP and anti-Sm antibodies in cSLE (4, 5). In our study, the proportion of antibodies, such as dsDNA, Sm, anti-RNP, SSA, SSB and APL, was significantly higher compared to adults. This finding supports the notion that cSLE is more active and associated with more inflammation processes than in aSLE patients. Previous studies have also reported renal involvement as a common feature in cSLE patients (19, 22). However, we found that renal involvement frequency did not significantly differ between cSLE and aSLE patients. Also consistent with other reports of China (7), it was significantly lower than reported in other regions, and the renal involvement was present in 71% of patients in the Philippines, 82% in Vietnam, and 86% in Thailand. One reason may be that the proportion of renal biopsy in our cohort was only 9%, compared

Table II. Clinical features of patients with different SLE onset ages and geographical areas.

	Present study	CSTAR (11)	Fiorot *et al.* (10)	Massias *et al.* (8)	Hiraki *et al.* (17)	Ramírez Gómez *et al.* (9)	Tan *et al.* (18)	Hoffman *et al.* (19)		
Geographical area	China	China	Brazil	UK	Canada	Latin America	Singapore	Belgium		
Patient	Children	Adults	Children	Children	Children	Children	Children	Children	$\chi^{2\#}$	$p^{\#}$
Number of patients	1020	2104	1312	422	256	230	64	56		
Female: male ratio	3.8:1	10.1:1	5.3:1	5.3:1	4.7:1	9.0:1	5.0:1	5.2:1	85.94	<0.001
Primary manifestation										
Rash	37.2%	53.8%	NA	NA	NA	NA	NA	NA	76.21	<0.001
Fever	33.4%	37.5%	NA	NA	NA	NA	NA	NA	4.9	0.026
Nephropathy	14.2%	25.8%	NA	NA	NA	NA	NA	NA	53.75	<0.001
Arthritis	13.6%	53.5%	NA	NA	NA	NA	NA	NA	453.6	<0.001
Haematocytopenia	12.7%	31.9%	NA	NA	NA	NA	NA	NA	132	<0.001
Clinical manifestation										
Malar rash	67.9%	47.9%	52.9%	NA	61.1%	70.4%	40.6%	69.6%	111.1	<0.001
Haematologic involvement	59.3%	56.1%	NA	45.5%	55.0%	NA	98.4%	NA	2.93	0.087
Fever	57.5%	37.5%	NA	NA	39.0%	63.5%	50.0%	67.3%		
Nephropathy	46.0%	47.4%	40.8%	31.5%	37.0%	49.1%	29.7%	62.5%	0.55	0.46
Arthritis	33.2%	54.5%	NA	NA	61.0%	83.1%	43.8%	59.3%	124.7	<0.001
Oral ulcers	16.4%	22.1%	33.5%	NA	21.0%	49.1%	26.6%	28.6%	13.9	<0.001
Neurologic involvement	13.2%	4.8%	11.0%	22.5%	16.0%	NA	NA	NA	69.98	<0.001
Photosensitivity	10.4%	25.0%	45.0%	NA	17.0%	53.0%	12.5%	44.6%	90.83	<0.001
Alopecia	8.0%	NA	NA	5.7%	22.0%	NA	31.3%	41.4%		
Fatigue	7.2%	NA	NA	NA	50.0%	NA	NA	78.6%		
Raynaud phenomenon	1.3%	NA	NA	NA	14.0%	NA	3.1%	39.3%		
SLEDAI										
<5	14.6%	25.3%	NA	NA	NA	NA	NA	NA	45.94	<0.001
5-9	39.0%	27.9%	NA	NA	NA	NA	NA	NA	39.35	<0.001
10-14	30.8%	28.1%	NA	NA	NA	NA	NA	NA	2.42	0.119
>14	15.6%	18.7%	NA	NA	NA	NA	NA	NA	4.51	0.034
Autoantibody-positive										
ANA	100.0%	98.1%	93.4%	94.3%	100.0%	96.9%	98.4%	100.0%	19.64	<0.001
dsDNA	61.3%	33.2%	59.5%	65.6%	72.0%	67.0%	90.6%	60.7%	221.3	<0.001
Sm	21.5%	16.6%	23.1%	21.8%	34.0%	51.3%	37.5%	17.9%	11.01	<0.001
anti-RNP	29.1%	8.9%	NA	NA	27	NA	45.3%	14.3%	1296	<0.001
SSA	40.5%	23.6%	NA	NA	27.0%	NA	53.1%	23.2%	94.68	<0.001
SSB	17.5%	10.7%	NA	NA	13.0%	NA	17.2%	7.1%	28.55	<0.001
APL(any)	62.3%	44.1%	16.5%	20.8%	32.0%	NA	39.1%	NA	209	<0.001

[#] Comparison of present study with CSTAR.

with 48% in the United States, 64% in Canada, and 78% in Egypt (23-25). Several studies have shown that urinary protein is not consistent with the type of renal perforation. Therefore, a kidney biopsy may meet the criteria for children with kidney damage without urinary protein reaching the diagnostic criteria of lupus nephritis. In addition, many guidelines recommend kidney biopsy as much as possible for cSLE with kidney damage.

Sjögren's syndrome (SS) is a systemic autoimmune disorder characterised by focal lymphocytic infiltration of the exocrine glands causing dry eyes and dry mouth. Primary SS is very rare in children and is mostly secondary to SLE. Some of the children in this study had parotid gland enlargement and submandibular gland enlargement which were typical clinical manifestations of SS. Six percent of the cSLE children who met the diagnostic criteria for SS were diagnosed with secondary Sjögren's syndrome in our cohort (26). There are regional differences in the clinical phenotype of cSLE. In our study, the gender ratio was F:M (3.8:1), similar to that in most regions, except the 9:1 for Latin America (9). Malar rash is the most common clinical manifestation, which is also common in other regions, but it is only present in 40.6% of patients in Singapore (18). The frequency of haematologic involvement seen in our cSLE cohort was similar to that reported in the UK and Canada (8, 17), and it was more prevalent than in Singapore (18). The proportion of lupus nephritis is similar to that reported in Latin America and Brazil (9, 10), but higher than that in Canada, Singapore, and the UK, and also lower than that found in Belgium (8, 17, 18). Moreover, the proportion of arthritis and the oral ulcer was significantly lower than that in aSLE of China and cSLE of other regions. The proportion of photosensitivity in this study was similar to that found in Singapore but lower than that described for Latin America, Brazil, Canada, the UK, and Belgium patients. Fatigue is only present in 7.2% of the patients in China, but it is as high as 50% and 78.6% in the reports of the UK and Belgium. It may be related to the fact that the clinician does not pay much attention to this clinical manifestation. The clini-

cal manifestations of Latin America are quite different from those in other regions, and the proportions of malar rash, fever, arthritis, oral ulcers, and photosensitivity are significantly higher than those in other regions (9).

The positive rates of dsDNA and Sm antibodies were similar to those in most other regions. However, the positive rates of dsDNA in Singapore and Sm in Latin America were higher than those in other countries (9). In addition, the positive rate of aPL in China is significantly higher compared to other countries, but the proportion of confirmed APS is not. The highest positive rate of aPL in our study was β 2 IgM. We hypothesise that it may be due to different detection methods in different regions. We studied and detected La, ACL IgG, ACL IgM, β 2-IgG, β 2-IgM,and β 2-igA, but other studies only describe some of them (8, 9, 17).

Our study has some limitations. Firstly, it is a single-centre study, and the data may be biased. Secondly, the retrospective design may miss some clinical and serological data.

In conclusion, this study is a large single-centre cohort study on cSLE from China and clarifies the clinical phenotype and autoantibody spectrum of children with cSLE for this population. Fever, rash, arthritis, and thrombocytopenia were the most common manifestations. Additionally, haematologic disorders and nephropathy were the most commonly involved organs. The clinical manifestations and autoantibody spectrum of cSLE are diverse, with regional and population differences.

Key messages

- In this large Chinese cSLE cohort, malar rash, fever, neurological involvement and several SLE autoantibodies were more common than in a Chinese aSLE cohort
- cSLE showed indications of higher SLEDAI score than aSLE.

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