

Systemic lupus erythematosus (SLE) in childhood: analysis of clinical and immunological findings in 34 patients and comparison with SLE characteristics in adults

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Abstract

Objective—To define the pattern of disease expression in patients with childhood onset systemic lupus erythematosus (SLE).

Methods—Prospective analysis of clinical manifestations and immunological features of 34 patients in whom the first manifestations appeared in childhood from a series of 430 unselected patients with SLE.

Results—Thirty one (91%) patients from the childhood onset group were female and three male (9%) (ratio female/male, 10/1, with no difference compared with the adult onset group). Mean age of this group at disease onset was 11 years (range 5–14) compared with 32 years (15–48) for the remaining patients. The childhood onset patients more often had nephropathy (20% *v* 9% in adult onset SLE, $p=0.04$; OR:2.7; 95%CI:1.1, 7), fever (41% *v* 21%, $p=0.006$; OR:2.6, 95%CI:1.2, 5.7), and lymphadenopathy (6% *v* 0.5%, $p=0.03$, OR: 12.3, 95%CI: 1.2, 127.6), as presenting clinical manifestations. During the evolution of the disease, the childhood onset patients had an increased prevalence of malar rash (79% *v* 51%, $p=0.002$; OR:3.7; 95%CI:1.5, 9.5) and chorea (9% *v* 0%, $p<0.0001$). This group exhibited a higher prevalence of anticardiolipin antibodies (aCL) of the IgG isotype when compared with the remaining patients (29% *v* 13%, $p=0.017$; OR:2.9, 95%CI:1.2, 6.8). No significant differences were found among the other antibodies between the two groups. Childhood onset patients more often received azathioprine (15% *v* 6%, $p=0.00004$; OR:11.2; 95%CI:2.8, 44.9) but no differences were detected between the groups concerning side effects or drug toxicity.

Conclusions—The presentation and the clinical course of SLE varied in this series of 430 patients depending on their age at disease onset. Nephropathy, fever, and lymphadenopathy were more common in childhood onset patients as presenting clinical manifestations, while malar rash, chorea, and detection of IgG aCL were more common during the evolution of the disease.

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Systemic lupus erythematosus (SLE) predominantly affects young women in reproductive age.¹ In 10–20% of patients, however, the diagnosis is made for the first time in childhood.²⁻⁶

Several investigators have reported that age at onset has a modifying effect on disease expression. This is important because examination of more homogeneous subsets, such as childhood onset patients, may allow for earlier diagnosis, better treatment, and more accurate prognosis. It has been noted that certain features of SLE usually associated with severity, such as nephritis or central nervous system dysfunction, are more common in patients with childhood onset SLE. In addition, serological abnormalities have also been reported to be different in childhood patients.²⁻⁶ However, the small number of patients that have been analysed in the different series, the disparity in selection criteria for patient inclusion, the age limits adopted, or the definition of the variables make comparison of findings in previous reports very difficult.

In this study, to better define the pattern of disease expression in childhood onset SLE patients, we have prospectively analysed the clinical manifestations and immunological features of 34 patients in whom the first manifestations appeared in the childhood from a series of 430 unselected patients with SLE.

Methods

PATIENT SELECTION

We studied prospectively 430 patients with SLE who were seen consecutively either as inpatients or outpatients between 1980 and 1995 and who were followed up by the same attending physicians (JF, RC, LP, MI). All were white and met the American College of Rheumatology (formerly American Rheumatism Association, ARA)⁷ revised criteria for SLE. In 34 (8%) the onset of disease, defined as the initial manifestation clearly attributable to SLE, occurred before the age of 14, and they represent the childhood onset group described in this report. The remaining 396 (92%) patients presented the initial manifestations after the age of 14, and they represent the adult onset group. All had medical histories documented and underwent medical interview as well as routine general physical examination by a qualified internist. A serum sample from each patient was collected for the immunological tests. Clinical and serological characteristics of all these patients were collected in a protocol

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Table 1 Clinical manifestations at the onset of SLE in the childhood onset patients compared with the adult onset patients

Manifestations	Childhood onset (n=34)	Adult onset (n=396)	p Value
	no (%)	no (%)	
Malar rash	15 (44)	139 (35)	NS
Discoid lesions	0 (0)	13 (3)	NS
Subacute cutaneous lesions	0 (0)	14 (3)	NS
Photosensitivity	8 (23)	80 (20)	NS
Oral ulcers	3 (9)	51 (13)	NS
Arthritis	22 (65)	247 (62)	NS
Serositis	4 (12)	51 (13)	NS
Nephropathy	7 (20)	35 (9)	0.04
Neurological involvement	0 (0)	26 (6)	NS
Thrombocytopenia	4 (12)	35 (9)	NS
Haemolytic anaemia	3 (9)	11 (3)	NS
Fever	14 (41)	83 (21)	0.006
Raynaud's phenomenon	4 (12)	62 (16)	NS
Livedo reticularis	1 (3)	2 (0.5)	NS
Thrombosis	0 (0)	3 (1)	NS
Myositis	1 (3)	15 (4)	NS
Lung involvement	0 (0)	5 (1)	NS
Chorea	1 (3)	0 (0)	NS
Sicca syndrome	0 (0)	2 (0.5)	NS
Lymphadenopathy	2 (6)	2 (0.5)	0.03

form. Salient features included in this protocol were: (1) age at onset of the disease, (2) age at diagnosis, defined as the age when the patient fulfilled four or more of the 1982 revised ARA criteria for the classification of SLE, (3) time of evolution of the disease, defined as the time from the onset until the present study, (4) clinical manifestations at the onset, (5) cumulative clinical manifestations during the evolution of the disease, and (6) laboratory features at diagnosis. Information collected into the protocol forms was transferred to a computerised database program (DBASE IV).

DEFINITION OF CLINICAL FEATURES

To minimise possible inter-observer bias, the variables of this protocol were carefully discussed by all the participating physicians on several occasions. The clinical manifestations evaluated in this protocol were defined according to the ARA glossary committee.⁸

LABORATORY STUDIES

Antinuclear antibodies (ANA) were determined by indirect immunofluorescence using

Table 2 Clinical manifestations during the evolution of SLE in the childhood onset patients compared with the adult onset patients

Manifestations	Childhood onset (n=34)	Adult onset (n=396)	p Value
	no (%)	no (%)	
Malar rash	27 (79)	203 (51)	0.002
Discoid lesions	5 (15)	17 (4)	NS
Subacute cutaneous lesions	1 (3)	25 (6)	NS
Photosensitivity	15 (44)	140 (35)	NS
Oral ulcers	13 (38)	100 (25)	NS
Arthritis	30 (88)	320 (81)	NS
Serositis	11 (32)	109 (27)	NS
Nephropathy	17 (50)	136 (34)	NS
Neurological involvement	9 (26)	63 (16)	NS
Thrombocytopenia	9 (26)	91 (23)	NS
Haemolytic anaemia	5 (15)	26 (6)	NS
Fever	21 (62)	170 (43)	NS
Raynaud's phenomenon	7 (20)	100 (25)	NS
Livedo reticularis	2 (6)	5 (1)	NS
Thrombosis	0 (0)	31 (8)	NS
Myositis	1 (3)	28 (7)	NS
Lung involvement	2 (6)	15 (4)	NS
Chorea	3 (9)	0 (0)	<0.001
Sicca syndrome	3 (9)	61 (15)	NS
Lymphadenopathy	2 (6)	3 (1)	NS

mouse liver as substrate and regarded as positive if higher than 1:100. Anti-dsDNA antibodies were determined with Farr's ammonium sulphate precipitation technique and considered as positive if higher than 7 U/ml. Precipitating antibodies to extractable nuclear antigens (ENA), including Ro(SSA), La(SSB), U1-snRNP and Sm were detected by counter-immunoelectrophoresis using calf and rabbit thymus and human spleen extracts. Rheumatoid factor (RF) was detected by latex test and regarded as positive if higher than 25 UI/ml. Anticardiolipin antibodies (aCL) of the IgG and IgM isotypes were measured by an ELISA method as described by Gharavi *et al*⁹ with minor modifications of our own.¹⁰ The results were expressed as negative or low, moderate, or high positive, according to the recommendations of the 1986 workshop on standardisation of the aCL test.¹¹ The lupus anticoagulant (LA) activity was detected by coagulation assays in platelet free plasma obtained by double centrifugation following the recommendations of the subcommittee on LA of the Scientific and Standardisation Committee of the International Society of Thrombosis and Hemostasis.¹²

STATISTICAL ANALYSIS

Conventional χ^2 and Fisher's exact tests were used for analysing qualitative differences, and Student's *t* test for comparison of means in large independent samples of similar variance. A $p < 0.05$ value was taken to indicate statistical significance. When several independent variables appeared to have statistical significance in the univariate analysis, a logistic regression test was performed for multivariate analysis to rule out possible confounding variables. In this case, only those variables showing statistical significance in the multivariate analysis were considered as significant in the results of the study. The odds ratio (OR) was calculated for assessing the risk of appearance of each variable. A lower limit of the 95% confidence intervals (CI) that exceeded 1.0 was taken to indicate statistical significance in the case of positive association and upper limit lower than 1.0 in the case of negative association. Results of the analysis of continuous variables are indicated as mean (SD). This statistical analysis was performed by means of the SPSS/PC 4.0 and EPIDAT programs using the information stored in the database program.

Results

PATIENTS

Thirty one (91%) patients from the childhood onset group were female and three male (9%) (ratio female/male, 10/1, with no difference compared with the adult onset group). Mean age of this group at disease onset was 11 years (range 5–14) compared with 32 years (15–48) for the remaining patients. Mean age at diagnosis of SLE of childhood onset patients was 14 years (range 6–28) compared with 34 years (15–85) for the adult onset patients. The interval between the time of onset and diagnosis was three years in the childhood onset group

Table 3 Immunological findings at diagnosis of SLE in the childhood onset patients compared with the adult onset patients

Variable	Childhood onset (n=34)	Adult onset (n=396)	p Value
	no (%)	no (%)	
Antinuclear antibodies	33 (97)	388 (97)	NS
High anti-dsDNA	29 (85)	360 (90)	NS
Anti-Ro (SSA)	5 (14)	82 (20)	NS
Anti-La (SSB)	2 (5)	26 (6)	NS
Anti-U1-snRNP	4 (11)	50 (12)	NS
Anti-Sm	4 (11)	49 (12)	NS
Rheumatoid factor	2 (5)	51 (12)	NS
IgG anticardiolipin antibodies	10 (29)	50 (13)	0.017
IgM anticardiolipin antibodies	6 (18)	34 (9)	NS
Lupus anticoagulant	6 (18)	57 (14)	NS

compared with two years in the adult onset group (difference not significant). Mean time of evolution of the disease in the childhood onset group was 85 months (range 1–264) and in the adult onset group was 73 months (1–528) (difference not significant).

CLINICAL MANIFESTATIONS

Table 1 shows the presenting clinical manifestations for patients with disease onset before or after age 14. The childhood onset patients more often had nephropathy (20% *v* 9% in adult onset SLE, $p=0.04$; OR:2.7; 95%CI:1.1, 7), fever (41% *v* 21%, $p=0.006$; OR:2.6, 95%CI:1.2, 5.7), and lymphadenopathy (6% *v* 0.5%, $p=0.03$, OR: 12.3, 95%CI: 1.2, 127.6). During the evolution of the disease (table 2), the childhood onset patients more often presented malar rash (79% *v* 51%, $p=0.002$; OR:3.7; 95%CI:1.5, 9.5) and chorea (9% *v* 0%, $p<0.001$). The frequency of other clinical features, including serositis, central nervous system manifestations and pulmonary disease, did not differ significantly between the groups.

IMMUNOLOGICAL FEATURES

Table 3 gives the main immunological findings of childhood onset patients. This group more frequently exhibited a positive level of anticardiolipin antibodies (aCL) of the IgG isotype when compared with the remaining patients

Table 4 Treatments prescribed for SLE during the study

Treatments	Childhood onset (n=34)	Adult onset (n=396)	p Value
	no (%)	no (%)	
NSAID	30 (88)	321 (81)	NS
Antimalarials	29 (85)	323 (82)	NS
Oral corticosteroids	32 (94)	332 (84)	NS
Pulse corticosteroids	1 (3)	3 (1)	NS
Oral cyclophosphamide	3 (9)	17 (4)	NS
Azathioprine	5 (15)	6 (2)	0.00004
Haemodialysis	0 (0)	1 (0)	NS
Antiaggregants	2 (6)	9 (2)	NS
Anticoagulants	0 (0)	16 (4)	NS

NSAID: Non-steroidal anti-inflammatory drugs.

Table 5 Main side effects because of the treatments prescribed for SLE during the study

Side effects	Childhood onset (n=34)	Adult onset (n=396)	p Value
	no (%)	no (%)	
Infections	6 (18)	39 (10)	NS
Osteoporosis	2 (6)	7 (2)	NS
Avascular necrosis	1 (3)	12 (3)	NS
Retinopathy	0 (0)	2 (0)	NS

(29% *v* 13%, $p=0.017$; OR:2.9, 95%CI:1.2, 6.8). No significant differences were found among the other antibodies between the two groups.

TREATMENT AND SIDE EFFECTS

Table 4 summarises the main SLE treatments prescribed during the study period. Childhood onset patients more often received azathioprine when compared with the remaining patients (15% *v* 6%, $p=0.00004$; OR:11.2; 95%CI:2.8, 44.9). No differences were detected between the groups concerning side effects or drug toxicity (table 5).

Discussion

There have been several studies dealing with childhood onset SLE and their results suggested that age at onset modifies the expression of the disease in terms of clinical presentation, pattern of organ involvement, and serological findings.^{2–6 13–33} However, the true prevalence of childhood onset SLE among the SLE population is unknown. One of the reasons is that there is not strict definition of childhood onset SLE. The most often used cut off ages are 14 or 16 years at onset of disease^{14–18} or at diagnosis.^{19 20} However several studies use a higher or lower cut off age. In our series, 34 (8%) of 430 patients with SLE developed the initial manifestations clearly attributable to the disease before the age of 14. In other series, the prevalence of childhood SLE in children younger than 16 is nearly 15%.^{14 15}

The onset of SLE is rare before the age of 5 years.¹³ In our series, one patient presented clinical manifestations of SLE at the age of 5 years but none of our patients presented these manifestations before this age.

The female to male ratio in adult onset SLE is generally found to be slightly more than 10:1. A higher proportion of men is often reported in childhood onset SLE in some series.^{14 20 21 26 27} but not in others.^{18 22 28} In our series, men represented 9% of the cases of childhood onset SLE with a female to male ratio similar to that in the adult onset SLE.

Although there are many previous publications of paediatric SLE, the strength of this study is that, unlike many others, it compares children and adults from the same clinic population. Comparison of the clinical features at onset between childhood onset and adult onset patients reveals both similarities and important differences. The frequency of skin, joint, serositis, and haematological disease was similar in both groups and correlates with previous reports.²⁰ However, childhood onset SLE patients had more frequently renal involvement, fever, and lymphadenopathy, as has also been reported by other authors.²¹

Nephropathy is often described in childhood onset SLE,^{22–24 26 27 32} although this manifestation has been more frequently described in North American series—especially in children with a Central and South American Hispanic background²³—than in European patients.¹ In our cohort, which includes all the patients diagnosed as having SLE in our areas, 20% of childhood onset SLE patients presented

nephropathy as initial clinical manifestation. Severity in this disease is closely related to renal involvement.^{6, 26, 33} Thus, SLE pattern is generally more severe in children than in adults. This inverse correlation between the severity of the disease and the age of diagnosis has been noted since the earlier series.²⁵ However, a striking finding is the additional organ system involvement over the course of follow up in both adults and children. As time goes on, prevalence of renal involvement is similar in both groups of age. The main significant differences during the evolution of the disease are the more common prevalence of malar rash and chorea in the childhood onset group, correlating with previous reports.¹⁵ It is of note that the treatment given to children was similar to that given to adults, except for a more common use of azathioprine in childhood onset patients. No differences were detected between the groups concerning side effects or drug toxicity.

Comparison of the autoantibody profiles of adults and childhood cases shows a similar frequency of increased anti-dsDNA and positive ANA in both groups. These data are in contrast with previous reports^{14, 31} in which the frequency of these antibodies is higher in childhood than adult cases. The only significant difference between the two groups is the higher presence of IgG aCL in children than in adult patients. However, there was not any case of thrombosis in childhood onset during the follow up period.

We conclude that the presentation and the clinical course of SLE varied in our series of 430 patients depending on their age at disease onset. Nephropathy, fever, and lymphadenopathy were more common in childhood onset patients as presenting clinical manifestations, while malar rash, chorea, and detection of IgG aCL were more common during the evolution of the disease.

- 1 Cervera R, Khamashta MA, Font J, Sebastiani GD, Gil A, Lavilla P, *et al.* Systemic lupus erythematosus: Clinical and immunologic patterns of disease expression in a cohort of 1,000 patients. *Medicine (Baltimore)* 1993;72:113–24.
- 2 Nepom BS, Schaller JG. Childhood systemic lupus erythematosus. *Prog Clin Rheumatol* 1984;1:33–69.
- 3 Tucker LB, Menon S, Isenberg DA. Systemic lupus in children: daughter of the Hydra? *Lupus* 1995;4:83–5.
- 4 Schaller J. Lupus in childhood. *Clin Rheum Dis* 1982;8:219–28.
- 5 Ting CK, Hsieh KH. A long term immunological study of childhood onset systemic lupus erythematosus. *Ann Rheum Dis* 1992;51:45–51.
- 6 Rosenberg AM. Systemic lupus erythematosus in children. *Springer Semin Immunopathol* 1994;16:261–79.
- 7 Tan EM, Cohen AS, Fries JF, Masi AT, McShane DJ, Rothfield NF, *et al.* The 1982 revised criteria for the classification of systemic lupus erythematosus. *Arthritis Rheum* 1982;25:1271–7.
- 8 American Rheumatism Association glossary committee. Signs and symptoms. *Dictionary of the Rheumatic Disease* 1982;1:1–80.
- 9 Gharavi AE, Harris EN, Asherson RA, Hughes GRV. Anticardiolipin antibodies: Isotype distribution and phospholipid specificity. *Ann Rheum Dis* 1987;46:1–6.
- 10 Cervera R, Font J, López-Soto A, Casals F, Pallarés L, Bové A, *et al.* Isotype distribution of anticardiolipin antibodies in systemic lupus erythematosus: prospective analysis of 100 patients. *Ann Rheum Dis* 1990;49:109–13.
- 11 Harris EN, Gharavi AE, Patel SP, Hughes GRV. Evaluation of the anti-cardiolipin antibody test: report of an international workshop held 4 April 1986. *Clin Exp Immunol* 1987;68:215–22.
- 12 Brandt JT, Triplett DA, Alving B, Scharrer I. Criteria for the diagnosis of lupus anticoagulants: an update. *Thromb Haemostasis* 1995;74:1185–90.
- 13 Dubois EL, Tuffanelli DL. Clinical manifestations of systemic lupus erythematosus. Computer analysis of 520 cases. *JAMA* 1964;190:104–13.
- 14 Costallat LTL, Coimbra AMV. Systemic lupus erythematosus: clinical and laboratory aspects to age at disease onset. *Clin Exp Rheumatol* 1994;12:603–7.
- 15 Huang DLT, Weschler B, Piette JC, Cacoub P, Sauvaget F, Papo T, *et al.* Clinical manifestations and outcome of childhood systemic lupus erythematosus: a retrospective study of 50 cases. *Eur J Int Med* 1993;4:15–22.
- 16 Hashimoto H, Tsuda H, Hirano T, Takasaki Y, Matsumoto T, Hirose S. Differences in clinical and immunological findings of systemic lupus erythematosus related to age. *J Rheumatol* 1987;14:497–501.
- 17 El-Garf A, Salah S. Juvenile systemic lupus erythematosus among Egyptian children. *J Rheumatol* 1990;17:1168–70.
- 18 Pande I, Sekharan NG, Kailash S, Uppal SS, Singh RR, Kumar A, *et al.* Analysis of clinical and laboratory profile in Indian childhood systemic lupus erythematosus and its comparison with SLE in adults. *Lupus* 1993;2:83–7.
- 19 Walravens PA, Chase HP. Prognosis of childhood systemic lupus erythematosus. *Am J Child* 1976;130:941–5.
- 20 Tucker LB, Menon S, Schaller JG, Isenberg DA. Adult- and childhood-onset systemic lupus erythematosus: A comparison of onset, clinical features, serology, and outcome. *Br J Rheumatol* 1995;34:866–72.
- 21 Meislin AG, Rothfield N. Systemic lupus erythematosus in childhood. *Pediatrics* 1989;83:235–9.
- 22 Glidden RS, Mantzouranis EC, Borel Y. Systemic lupus erythematosus in childhood: clinical manifestations and improved survival in 55 patients. *Clin Immunol Immunopathol* 1983;29:196–210.
- 23 Caeiro F, Michielson FMC, Bernstein R, Hughes GRV, Ansell BM. Systemic lupus erythematosus in childhood. *Ann Rheum Dis* 1981;40:325–31.
- 24 Celemeyer DS, Thorner PS, Baumal R, Arbus GS. Sex differences in childhood lupus nephritis. *Am J Dis Child* 1984;138:586–8.
- 25 McCombs RP, Patterson JF. Factors influencing the course and prognosis of systemic lupus erythematosus. *N Engl J Med* 1959;260:1195–204.
- 26 King KK, Kornreich HK, Bernstein BH, Singens BH, Hanson V. The clinical spectrum of systemic lupus erythematosus in childhood. *Arthritis Rheum* 1977;20:287–94.
- 27 Cassidy JT, Sullivan DB, Petty RE, Ragsdale C. Lupus nephritis and encephalopathy: Prognosis in 58 children. *Arthritis Rheum* 1977;20:315–22.
- 28 Lehman TJA, McCurdy DK, Bernstein BH, King KK, Hanson V. Systemic lupus erythematosus in the first decade of life. *Pediatrics* 1989;83:235–9.
- 29 Yancey CL, Doughty RA, Athreya BH. Central nervous system involvement in childhood systemic lupus erythematosus. *Arthritis Rheum* 1981;24:1389–95.
- 30 Shergy WJ, Kredich DW, Pisetsky DS. Patterns of autoantibody expression in pediatric and adult systemic lupus erythematosus. *J Rheumatol* 1989;16:1329–34.
- 31 Ward MM, Dawson DV, Kredich DW, Pisetsky DS. Expression of IgM and IgG autoantibodies in pediatric and adult systemic lupus erythematosus. *Clin Immunol Immunopathol* 1990;55:273–84.
- 32 Barron KS, Silverman DE, Gonzales J, Reveille J. Clinical, serologic and immunogenetic studies in childhood-onset systemic lupus erythematosus. *Arthritis Rheum* 1993;33:340–8.
- 33 Tejani A, Nicastrì AD, Chen CK, Fikrig S, Gurumurthy K. Lupus nephritis in Black and Hispanic children. *Am J Dis Child* 1983;137:481–4.