

Systemic lupus erythematosus in childhood

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SUMMARY The clinical and serological features have been analysed retrospectively in 42 patients with an onset of systemic lupus erythematosus (SLE) up to 16 years of age. Thirty-seven (88.1%) were female and 5 (11.9%) male. The mean age of onset was 12.3 years (range 7-16); 11 patients were 10 years or under. The mean duration of disease from diagnosis was 7.1 years (range 6 months-25 years). There were 6 deaths, 3 from infection, 2 from renal failure, and 1 from heart failure. Survival was calculated both from the date of onset and from the date of diagnosis. With the latter the estimated overall survival at 5 years was 82.6% and at 10 years 76.1%. The survival for patients with lupus nephritis was 59.5% at 5 years and 47.6% at 10 years. These data suggests that SLE in childhood is not necessarily associated with a poor prognosis, though renal involvement is still serious. There appeared to be no major differences between prepubertal, adolescent, and adult SLE with respect to clinical and serological findings.

Reports on childhood SLE in the past 25 years have provided conflicting views on its course and prognosis.¹⁻¹⁰ During the past decade a more widespread awareness of the disease, as well as the development of newer diagnostic techniques, has led to a recognition that the course and overall prognosis of SLE is less grave than previously thought.^{8, 10-13} The aims of this study were to analyse retrospectively the clinical and laboratory findings and prognosis in childhood systemic lupus erythematosus.

Patients and methods

Forty-two patients whose disease developed at the age of 16 or under were included in this study. They had been seen at the Canadian Red Cross Memorial Hospital, Taplow (26 cases), between 1948 and 1980, and at the Hammersmith Hospital, London (16 cases), between 1956 and 1980. Patients were included only when at least 4 of the preliminary criteria established by the American Rheumatism Association were present.¹⁴ Patients with drug-induced lupus, discoid lupus, and mixed connective tissue disease were excluded. The follow-up was from 7 months to 28 years after disease onset, the

first symptom clearly attributable to SLE being taken as the time of onset of the disease (mean 8.1 years), and 5 months to 25 years from the time of diagnosis (mean 7.1 years). Survival was calculated by the method of Merrell and Shulman.¹⁵ Statistical significance was determined by the method of Gribetz and Benley.²

Results

Of the 42 children 37 were female (88.1%) and 5 male. Forty children were Caucasian, 1 Kenyan Indian, and 1 Negro. The mean age of onset was 12.3 years and the mean age at diagnosis was 13.5 years. The mean time between estimated onset and diagnosis was 1.2 years, with the longest time between onset and diagnosis 11 years. The number of patients with an onset of disease at 10 years of age or less was 11 (26.1%), 31 being aged 11 or more; all the males belonged to the latter group. The peak age of onset was at 14 to 15 years of age for girls (Fig. 1).

The initial manifestations are shown in Table 1. Arthritis and/or arthralgias (38%), rash (21%), and fever (16%), were the commonest presenting symptoms. Other forms of presentation included haemolytic anaemia in 4 patients, thrombophlebitis in 2, and nephritis, serositis, vasculitis, seizures, alopecia, and Raynaud's phenomenon in 1 patient respectively. Fifteen of the children (35.7%) had

Accepted for publication 13 October 1980.

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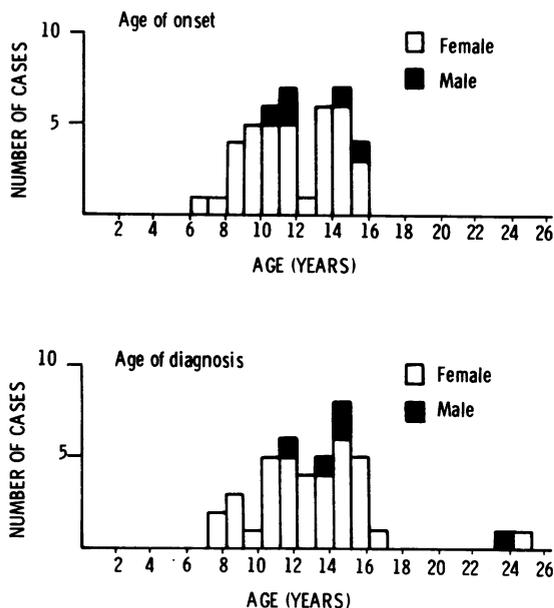


Fig. 1 Age at onset and at diagnosis in 42 children with SLE.

Table 1 Initial manifestation in 42 children with SLE

Manifestations	Per cent
Arthritis or arthralgias	38
Rash	21
Fever	16
Haemolytic anaemia	9
Thrombophlebitis	9
Nephritis	2
Serositis	2
Vasculitis	2
Seizures	2
Alopecia	2
Raynaud's phenomenon	2

Table 2 Initial diagnosis (other than SLE) in 42 children with SLE

Diagnosis	Number
Juvenile chronic arthritis	5
Haemolytic anaemia	4
Rheumatic fever	2
Idiopathic thrombocytopenia	1
Hodgkin's disease	1
Thrombophlebitis	1
Migraine	1

been initially diagnosed as having diseases other than SLE, summarised in Table 2, notably juvenile chronic arthritis in 5, haemolytic anaemia in 4, rheumatic fever in 2, recurrent thrombophlebitis in 2, and Hodgkin's disease, idiopathic thrombocytopenia, and migraine in 1 case respectively. In 8

Table 3 Major clinical features in 42 children with SLE

Clinical features	Per cent
Arthritis or arthralgias	100
Rash	76.1
Fever	54.7
Alopecia	54.7
Vasculitis	54.7
Nephritis	47.6
Lymphadenopathy	40.4
Pleurisy	35.7
Raynaud's phenomenon	30.9
Psychosis	30.9
Photosensitivity	28.5
Neurological	26.1
Pericarditis	23.8
Oral/nasal ulcers	19.0
Splenomegaly	19.0

cases a severe sore throat preceded the onset of the disease by some weeks; in one, streptococcal infection was identified and in another monilia and streptococci. Precipitation of the disease by sun exposure was suggested in 3 patients.

The major clinical features found in the present series are listed in Table 3. Analysis of the clinical manifestations in those under and over 10 years revealed no significant differences between the 2 groups; therefore they are reviewed together.

Musculoskeletal manifestations. Polyarthrits (or arthralgias) occurred in 42 patients (100%) and was the initial symptom in 38%. In 1 case the disease presented as a monoarthrits in the knee. Deforming arthrits (Jaccoud's) was found in 4 patients (9.5%).¹⁶ Four patients presented with tendon contracture leading to flexion of the fingers. Proximal muscle weakness was found in 6 children (14.2%). Aseptic necrosis of the hip and vertebral collapse were respectively seen in 2 patients who had been on high dose corticosteroid therapy.

Skin and mucocutaneous manifestations. Rashes were present in 32 children (76.1%). Twenty-one (50%) had the typical 'butterfly' rash, 2 a generalised rash, and in 9 the rash was confined to the limbs. Photosensitivity was found in 12 patients (28%). Alopecia occurred in 23 (54.7%) but was an initial symptom in only 1 case. Oral ulcers were seen in 8 children (19%). Thirteen patients (30.9%) had Raynaud's phenomenon. While this was usually mild, 2 patients developed severe Raynaud's phenomenon with finger-tip ischaemia. Various forms of vasculitis (digital vasculitis, nail-fold infarcts, palmar and plantar rashes, and skin ulcerations) were found in 23 patients (54.7%). Purpura was present in 7 cases (16.6%) and in 3 it was associated with thrombocytopenia. Discoid lesions were found in 3 patients (7.1%). One patient developed small elbow nodules, the histology of which was similar to a rheumatoid nodule.¹⁵

Pulmonary manifestations. The commonest finding was pleurisy or pleural effusion, seen in 13 patients (30.9%). Diffuse pulmonary infiltrates, which were unresponsive to antibiotics but improved with corticosteroids, were noted in 4 patients. Bacterial pneumonia developed in 2 cases and in 1 was the cause of death. The most common radiological findings were high diaphragm, pleural thickening, linear shadows in the bases, and interstitial infiltrates. Pulmonary function tests were abnormal in more than one-half of the patients tested. As in adults the abnormalities consisted mainly of a restrictive defect and a low lung diffusion capacity.¹⁷

Cardiac manifestations. The commonest cardiac manifestation was pericarditis, seen in 10 patients (23.8%). In 5 of the 10 the pericarditis was associated with pleurisy. One patient had a clinical diagnosis of myocarditis and another patient died of cardiac failure associated with hypertension and renal failure; this patient at necropsy also had a Libman-Sachs endocarditis. Seven patients were hypertensive (diastolic pressure greater than 95 mmHg), and 3 of these patients had renal failure.

Renal manifestations. Renal involvement was defined by the presence of haematuria (5 or more red blood cells per high power field), or cellular casts in the urine, proteinuria of 1 g or greater per 24 hours, serum creatinine >150 $\mu\text{mol/l}$, or presence of histological changes compatible with SLE on renal biopsy.¹⁸ On these criteria lupus nephritis was present in 20 of the 42 children (47.6%) and 8 patients had impairment of renal function at our first assessment. Twelve of 17 patients (70.5%) with lupus nephritis who were tested had low serum complement (C3), but 12 of 18 patients tested (66.6%) without nephritis also had a low level of serum complement.

Neurological manifestations. These had occurred in 11 patients (26.1%). Grand mal seizures were the most frequent manifestation, 8 patients (19.0%), 6 without and 2 with renal failure. One patient had an episode of homonymous hemianopia associated with severe headaches. Bilateral facial palsy was present in 1 patient and peripheral neuropathy in another. Headaches of clinical significance were observed in 6 patients. Moderate to marked electroencephalographic (EEG) abnormalities were seen in 7 patients of 8 tested (diffuse abnormality in 4 patients and focal abnormality in 3). Technetium brain scanning was abnormal in only 2 patients of 7 tested and oxygen-15 scanning was abnormal in 6 of 8 patients tested.¹⁹

Severe psychoneurosis (phobias and depression) and psychosis (schizophrenia and depressive states) were the most frequent psychiatric manifestations,

occurring in 12 patients (28.5%) during the course of the disease. The minor psychiatric abnormalities (anxiety states and mild depression) and psychosis attributed to steroid therapy were not included in this figure.

Reticuloendothelial system. Lymphadenopathy was present in 17 patients (40.4%)—in these under 10 tended to be generalised. Splenomegaly occurred in 8 patients (19.0%).

Haematological manifestations. Anaemia (Hb less than 11 g/dl) was present in 22 patients (52.3%) and a positive direct Coombs test was noted in 7 of 11 patients tested (63.6%). In 4 haemolytic anaemia was the first symptom of the disease. Leucopenia (total leucocyte counts less than $4.0 \times 10^9/\text{l}$) was noted in 22 patients (52.3%). Thrombocytopenia (platelets less than $100 \times 10^9/\text{l}$) was present in 12 of the 42 patients (28.5%). All these values were noted before the administration of any drugs likely to depress bone marrow function.

Laboratory findings. All the patients had a raised ESR at presentation with a mean value of 56 mm in 1 hour and a median of 50 mm. The C-reactive protein (CRP) levels of 22 patients tested were low or moderately elevated, with a median of 1 $\mu\text{g/ml}$; there was no correlation between the levels of CRP and ESR (Fig. 2). At the time of diagnosis anti-nuclear antibodies were detected in 100% of the 36

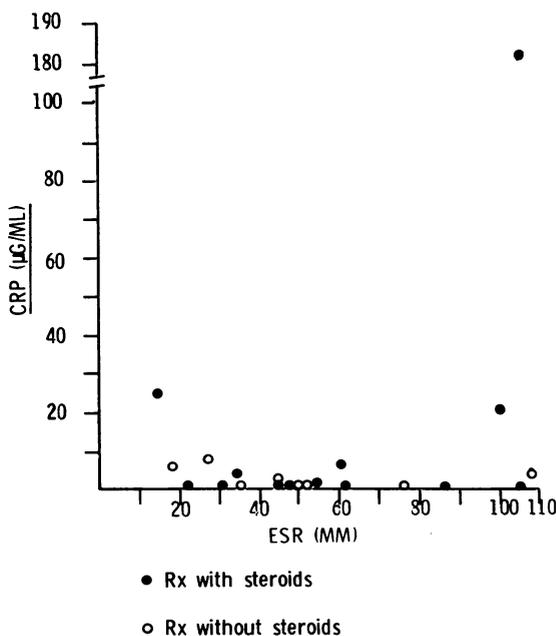


Fig. 2 Correlation between C-reactive protein (CRP) and Westergren ESR levels in 21 children with SLE.

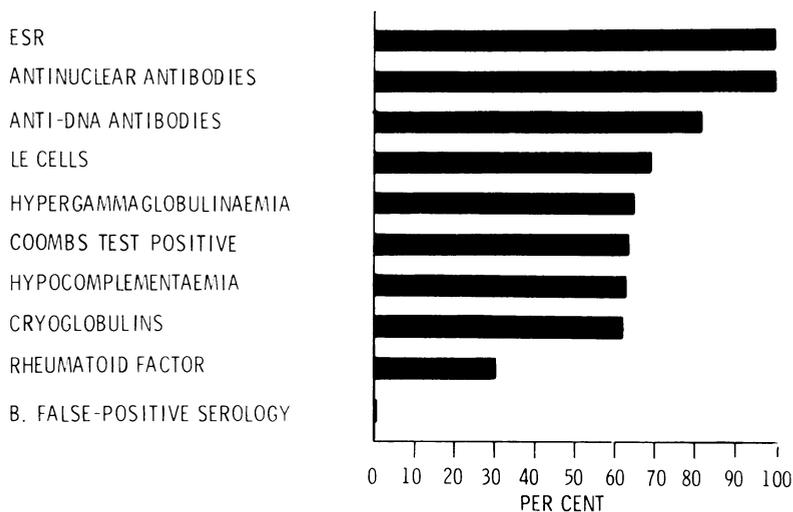


Fig. 3 Laboratory findings in 42 children with SLE.

patients tested; anti-DNA antibodies were found in 81.8% of 33 patients tested. The LE cell test was positive in 69% of 39 patients tested. The rheumatoid factor (latex) was present in 31% of the patients. Hypergammaglobulinaemia was observed in 64.8% of 37 patients tested, and 1 patient had IgA deficiency. Hypocomplementaemia was present in 62.8% of 35 patients tested, and 5 of 8 patients tested had cryoglobulinaemia (Fig. 3).

Treatment. Of the 42 patients 40 had received prednisolone or the equivalent, initially in doses of 40–30 mg/day and then tapered gradually to a dosage adequate to control the disease clinically. Hydroxychloroquine in a dose of 200 mg/m²/day was used in 9 patients. Fifteen patients received immunosuppressive drugs in the form of azathioprine (2 mg/kg/day) in 10 patients either for renal disease (8) or vasculitis (1) or central nervous system involvement (1). Cyclophosphamide (2–2.5 mg/kg/day) was administered to 5 patients, and all had renal involvement with severe systemic disease. Plasmapheresis was used in only 3 patients, all of whom had nephritis and systemic disease.

Prognosis. The 42 patients were followed up for periods of one-half to 25 years following diagnosis (mean duration 7.1 years). There were 6 deaths (14.2%), 4 of females and 2 of males, all occurring within the first 6 years of the disease. Infection (septicaemia, pneumonia, gangrene of the leg) in association with active SLE and corticosteroid treatment was the cause of death in 3 patients. Renal failure was the terminal event in 2 patients and heart failure and hypertension associated with renal failure in 1 (Table 4). At the present time, of the

Table 4 Causes of death and duration of disease in 6 fatal cases of children with SLE

Cause of death	Number	Mean duration of disease from diagnosis to death in years
Infection	3	4.6
Sepsis	1	3.0
Pneumonia	1	6.0
Gangrene	1	5.0
Renal failure	2	1.0
Heart failure	1	3.0

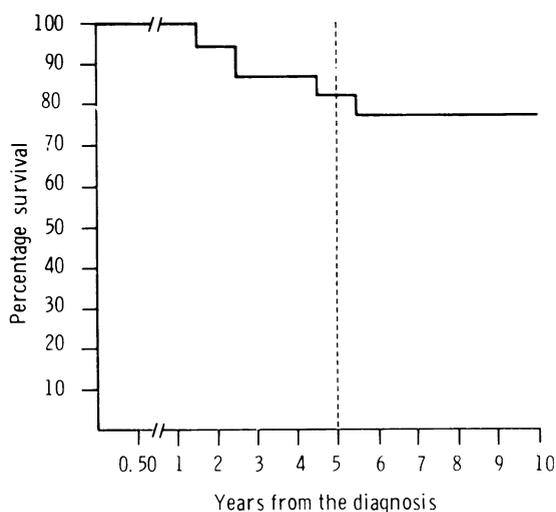


Fig. 4 Survival curve from diagnosis in 42 children with SLE.

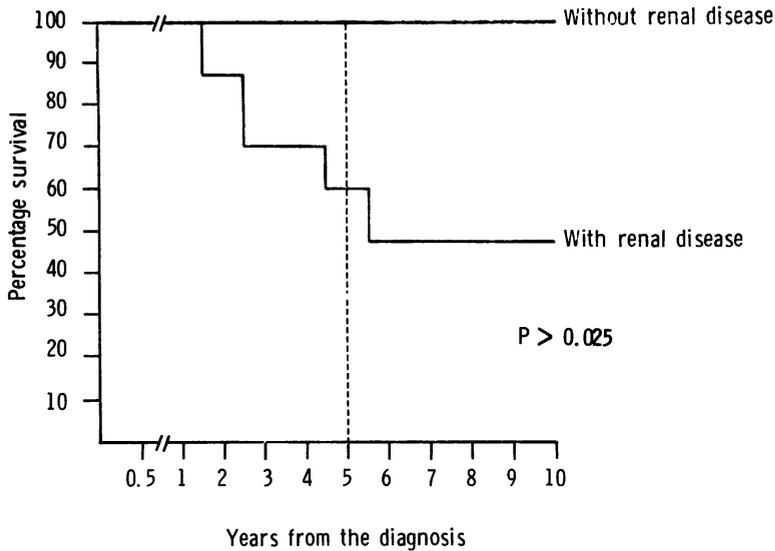


Fig. 5 Survival curve from diagnosis in 42 SLE children with and without renal disease.

surviving 36 patients 4 are in remission needing no medication, 15 are either asymptomatic or have mild symptoms and are being maintained on small doses of corticosteroids (less than 10 mg of prednisolone a day). Twelve patients with active disease are receiving higher doses of corticosteroids (more than 10 mg of prednisolone a day in 5 cases and/or immunosuppressive drugs in 7 cases). Five patients have been lost to follow-up. Survival was calculated from the time of diagnosis as the starting point.¹⁵ The estimated survival for the whole group of patients at 5 years was 82.6% and at 10 years 76.7% (Fig. 4). From the first symptom as starting point the estimated 5-years survival was 86% and 10-years survival was 76.8%. Two deaths occurred within the first year of diagnosis, 2 in the second year, and 1 each in the fourth and fifth years. Estimated survival rates for patients with and without renal involvement differed strikingly. From the time of the diagnosis as the starting point no deaths occurred in the non-nephritic group. In the group with nephritis the 5-years survival was of 59.5% and the 10-years survival 47.6% ($0.025 > /2 > 0.010$) (Fig. 5). The estimated 5-years survival for the males was 47.6% and for females 83%, but this difference was not statistically significant because of the small number of males analysed.

Discussion

These data suggest that the pattern of disease and the prognosis of SLE in childhood is similar to that

in adults. Perhaps the most striking finding is the 100% 10-years survival in the 'non-renal' group. Even when allowance is made for the selection bias inherent in partly retrospective analysis, this improved prognosis mirrors that seen in more recent series of adult patients.¹¹⁻¹³ The peak age of onset reached during adolescence was the same as that found by Reislin and Rothfield⁶ and Estes and Christian.¹¹ All the males of this series belonged to the group of patients who developed SLE after 10 years of age and it did not confirm the higher proportion of males in the younger age group reported by King *et al.*⁹ and Kornreich *et al.*⁷ In general, SLE appears to be rare before the age of 5 years.^{11 20} The finding in our series of 5 patients with a previous diagnosis of juvenile chronic arthritis confirms the diagnostic problems noted also by Ragsdale *et al.*,²¹ who described 10 patients with juvenile rheumatoid arthritis who developed clinical manifestations of SLE in 2½ to 21 years later. These workers suggested that SLE may account for as many as 3% of children in whom the initial diagnosis was juvenile rheumatoid arthritis or Still's disease.

As in studies of adult cases and other studies of SLE in children, arthritis and/or arthralgia was the commonest manifestation, followed by rash and fever. Some investigators have claimed that splenomegaly and lymphadenopathy occur much more frequently in children than in adults,^{6 9} but this was not so in the present series.

We found a higher incidence of a positive Coombs test (63.6%) than in adults,¹³ but this may have been due to selection bias. The levels of CRP in patients

with active disease were low or modestly raised, as has been shown in adult patients with SLE.²²⁻²⁴ The median CRP level was 1 µg/ml. There were no differences between the median of patients treated with and without steroids. Recently it has been suggested that CRP may be of value in the differential diagnosis of patients with polyarthritis, and that CRP levels should be considered in future classification criteria for SLE.²⁵ The present study also suggests that CRP estimations might be of value in the differential diagnosis of polyarthritis in children.

Anti-DNA antibodies were found in 81.8% of these patients. Pincus *et al.*²⁶ previously noted the presence of anti-DNA antibodies in 91% of a group of children with SLE, and Hughes *et al.*²⁷ described high DNA-binding activity in 2 of 18 patients with juvenile rheumatoid arthritis both of whom subsequently developed SLE. Thus the determination of DNA-binding may also be of value in the differentiation of SLE in children from other forms of polyarthritis, except when they are on treatment with penicillamine.

IgA deficiency was seen in 1 of our patients; Cassidy *et al.* have suggested that this can occur in as many as 4.6% of SLE patients.²⁸

Some authors have shown a higher mortality for children during the first year after diagnosis,⁶ while others,⁹ including ourselves, have shown an even distribution of mortality over the first 5 years. Infection associated with active disease was the main cause of death and renal failure the second most frequent. Four of the 6 deaths occurred before 1956. The lower mortality during the last 24 years is likely to be due in part to the development of new diagnostic tests, better management of the disease, and the use of antibiotics and immunosuppressive drugs.

From the time of diagnosis as the starting point the survival curve for the whole group at 5 years was 82.6% and at 10 years 76.7%. The development of renal disease had a marked influence on the survival, though death was not necessarily due to renal failure. In the group with renal involvement the 5-years survival was 58.5% and the 10-years survival 47.6%. There were no deaths in the group without renal disease. These findings are in agreement with those of other series which showed that renal involvement at the time of diagnosis reduced survival.^{3 6 29-31}

It is concluded that SLE, while exceptionally rare in children under 5 years of age, is an important differential diagnosis in the polyarthritis of adolescents, particularly girls. Although prognosis is markedly affected by the early development of nephritis, the improved survival now compares favourably with that seen in adults.

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