Lupus (2007) 16, 550–555
http://lup.sagepub.com

PAPER

Distinctive clinical features of pediatric systemic lupus erythematosus in three different age classes

FR Pluchinotta, B Schiavo, F Vittadello, G Martini, G Perilongo and F Zulian*
Dipartimento di Pediatria, Università di Padova, Via Giustiniani 3, 35128 Padova, Italy

It is estimated that around 20% of patients with systemic lupus erythematosus (SLE) have their onset in childhood but there have been conflicting data about the prevalence and severity of the clinical features in different age classes. We conducted this study to analyse the clinical features of patients with pediatric SLE (pSLE) with onset in infancy, prepubertal and postpubertal age.The charts of patients followed at the Department of Pediatrics, University of Padua, who met the criteria for SLE diagnosis, were reviewed. Patients were divided into three groups based on age at disease onset: group A, patients ≤2 years old, group B patients aged between 2 and 10 years, group C patients between 11 and 16 years of age. The clinical and laboratory characteristics of each group were compared. Forty-two patients with pSLE entered the study: 2 were diagnosed before the age of 2 years, 11 between 2 and 10 years and 29 between 10 and 16 years. Eleven more patients with infantile (onset <2 years) SLE (iSLE) were found by a systematic literature search on PubMed and EmBASE and added for analysis to the group A. The female preponderance was significant only in postpubertal patients (F:M = 6.3: 1) whereas the other two groups presented a similar F:M ratio (1.2: 1). In comparison with the other two groups, iSLE showed a significantly higher prevalence of cardiovascular and pulmonary involvement, anemia and thrombocytopenia and a shorter disease duration at time of diagnosis. The postpubertal group showed a higher frequency of musculoskeletal involvement and leukopenia. In prepubertal patients there was no female preponderance and the frequency of clinical features was intermediate between infantile and postpubertal patients. Complement fractions level, antinuclear antibodies (ANA), anti-dsDNA, anti-cardiolipin antibodies and lupus anti-coagulant autoantibodies were not significantly different in the three groups. In general, the prevalence of internal organs involvement in pSLE seems to decrease with age. In infants, SLE is more severe than in the following ages. Postpubertal patients have a strong female preponderance and more specific signs of disease at onset. Prepubertal patients have an intermediate disease severity and no gender predilection. *Lupus* (2007) **16**, 550–555.

Key words: child; infant; outcome; systemic lupus erythematosus

Introduction

Systemic lupus erythematosus (SLE) is a multisystem autoimmune disease characterized by a variable clinical picture and serological abnormalities. The clinical course can range from mild to severe and be potentially life-threatening. Most studies of SLE in childhood include few patients less than 10 years of age.[1–5]

We compared the clinical and laboratory differences between early and late onset of pediatric SLE to find whether different cutoff ages may have some relevance in clinical presentation and outcome.

Methods

Study design and patient selection

The charts of patients from the Pediatric Rheumatology Unit, University of Padua, who met the criteria for SLE (American College of Rheumatology) were reviewed.[6,7]

Patients were divided into three groups based on age at disease onset: group A included patients ≤2 years, infantile SLE (iSLE), group B patients were between 2 and 10 years (pre-pubertal), group C patients were between 11 and 16 years old (postpubertal). The clinical and laboratory characteristics of each group were compared.

*Correspondence: Francesco Zulian, MD, Dipartimento di Pediatria, Università di Padova, Via Giustiniani 3, 35128 Padova, Italy. E-mail: zulian@pediatria.unipd.it

10.1177/0961203307080636

Data collection

The following parameters have been considered for each patient at the time of diagnosis: age, sex, ethnicity, family history positive for autoimmune conditions in first and second degree relatives, disease duration at diagnosis, clinical and laboratory characteristics at diagnosis and outcome. Clinical manifestations include involvement of skin, mucosal membrane, joints, lymph nodes, spleen, kidney, lung, heart, gastrointestinal and central nervous systems.

The criteria for renal involvement included the presence of either proteinuria (>10 mg/kg/day or $>++$ dipstick testing) and/or significant hematuria in the urinalysis or elevated serum creatinine. The renal lesions at biopsy were classified according to WHO classification system modified by the International Study of Kidney Diseases in Children.[8] Musculoskeletal disease included the presence of arthralgia, arthritis or myositis. Positive mucocutaneous involvement included the presence of malar rash, discoid lupus, oral ulcers or alopecia.

Laboratory investigations, considered at the time of diagnosis, include: white blood cell count (WBC), hemoglobin and complement fractions C3 and C4. These parameters were considered to be abnormal if greater or lower than 2 SD values for age.[9] Platelet count was considered abnormal if lower than $150 \times 10^3/mm^3$. ANA and anti-dsDNA antibody titers were considered positive when the first was $>1:80$ on Hep-2 cell line, and the latter $>1:40$ on counterimmunoelectrophoresis. Presence of anti-cardiolipin antibodies (aCL), IgM or IgG was detected by ELISA while lupus anti-coagulant (LAC) was detected by the activated partial thromboplastin time the kaolin clotting time and the dilute Russell's viper venom time. In order to evaluate the disease activity at diagnosis we considered the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) score.[10] We considered also the mortality rate with disease duration and cause of death.

In order to find cases of infantile SLE (iSLE) with onset during the first two years of life, a systematic literature search on PubMed and EmBASE was performed. Case reports or case series reporting patients with iSLE were analysed according to the clinical and laboratory parameters previously described.

Statistical analysis

Descriptive statistics were used for clinical and laboratory parameters. Clinical and laboratory findings and outcome from the three groups of patients were compared by Chi-square test (χ^2) and Fisher-Freeman-Halton exact test. The differences in time interval between onset of disease and diagnosis and cumulative disease activity were evaluated by one-way analysis of variance and least significant difference multiple comparisons test. A P-value <0.05 was considered significant.

Results

Patients

From the charts review of the SLE patients followed at the Rheumatology Unit of the Department of Pediatrics of Padua, two patients with disease onset during the first two years of life and 40 between 2 and 16 years were found. Eleven more patients with iSLE, reported in case series or case reports from 1975 and 2005, have been found by the literature search.[11–20]

The clinical characteristics of pSLE patients are summarized in Table 1.

Thirteen patients had their disease onset during the first two years of life, 11 children had SLE diagnosed prior to their 11th birthday and in 29 patients disease was diagnosed between their 11th and 16th birthday. There were 38 females (71.7%) and 15 males (28.3%). The female to male ratio was ~1.2 in group A and B, respectively, and 6.3 in group C. Thus, in comparison with group A and B, group C showed a significant higher prevalence of females ($P = 0.035$).

In group A ten patients were Caucasian, one African-American and for two the ethnicity was not specified; in group B one was Indian and all the others were Caucasian; in group C all patients were Caucasian.

A family history positive for autoimmune diseases was present in 46.2% of group A patients, 25% of group B and 28.6% of group C.

In group A, the age at disease onset ranged from 1 to 11 months (mean 6, median 5 months), in group B from 25 to 130 (mean 83 months, median 94 months) and in group C from 133 to 192 months (mean and median, 150 months)

The time interval between onset of disease and diagnosis was significantly shorter in group A patients (mean 0.7, range 0–3 months) versus both group B (mean 6.3, range 1–20 months) and C (mean 6.7, range 1–33 months).

Clinical features

The frequency of the various clinical manifestations and laboratory features at the time of diagnosis was different among the three groups of patients.

The prevalence of mucocutaneous, gastrointestinal and reticuloendothelial (lymphadenopathy and hepatosplenomegaly) involvement were similar in the three age classes.

The musculoskeletal involvement was very uncommon in infants and more common in children and

Table 1 Clinical and laboratory characteristics of the three groups at diagnosis

Characteristics	*Group A (n = 13)*	*Group B (n = 11)*	*Group C (n = 29)*	*Significance (2 tails)*
Gender (F : M)	1.2:1	1.2:1	6.3:1	$P < 0.05$
Ethnicity (%)	Caucasian 10 (77) Afro-american 1 (8) Unknown 2 (15)	Caucasian 10 (91) Indian 1 (9)	Caucasian 29 (100)	
Positive family history (%)	6 (46.2)	2 (25)	8 (28.6)	ns
Mean disease duration at diagnosis (months)	0.7	6.3	6.7	$P < 0.0001$
Organ involvement (%)				
Mucocutaneous	6(46.1)	6(54.5)	19 (65.5)	ns
Musculoskeletal	3(23.1)	5 (45.5)	22 (75.9)	$P < 0.005$
Lymph nodes	7(53.8)	5 (45.5)	13 (43.4)	ns
Spleen	7(53.8)	5(45.5)	9 (31)	ns
Renal	12 (92.3)	7(63.6)	17 (58.6)	ns
Central nervous system	6 (46.2)	2(18.2)	6 (20.7)	ns
Gastrointestinal	6(46.2)	4 (36.40)	12 (41.4)	ns
Respiratory	6 (46.2)	2 (18.2)	4 (13.8)	$P< 0.05$
Cardiovascular	4 (30.8)	1 (9.1)	1 (3.4)	$P <0.05$
Laboratory (%)				
Leukopenia	1 (7.7)	1 (9.1)	9 (31)	ns
Anemia	10 (76.9)	5 (45.5)	9 (31)	$P < 0.05$
Thrombocytopenia	9 (69.2)	1 (9.1)	9 (31)	$P < 0.01$
Low C3	9 (69.2)	8 (72.7)	21 (72.4)	ns
Low C4	9 (69.2)	6 (54.5)	16 (55.2)	ns
Autoantibodies positive/ tested (%)				
ANA	12/13 (92.3)	11/11 (100)	29/29 (100)	ns
ds-DNA	11/12 (91.7)	8/11 (72.7)	20/29 (69)	ns
aCL	3/6 (50)	4/8 (50)	11/22 (50)	ns
LAC	1/4 (25)	0/7 (0)	7/21 (31.8)	ns

teenagers where it was found in three-quarters of the patients.

Conversely, infants showed a significantly higher prevalence of cardiovascular involvement. The most common manifestation was Libman-Sachs endocarditis (2 patients), associated with congestive heart failure in one patient, followed by left ventricular hypertrophy and pericarditis each observed in one patient. Pericarditis was the only cardiac manifestation in group B and C.

Pulmonary manifestations were quite severe and more frequent in infants when compared with the other two groups, but not significantly. In the infant group, in fact, 2 out of 6 patients presented pulmonary hemorrhage, leading to death in one of them. Groups B and C had the same frequency of the pulmonary manifestations, including pulmonary alveolitis or pleural effusion.

Evidence of renal disease was present at diagnosis in 44 patients (83%), 20 of whom had hypertension. Interestingly, the frequency of renal involvement decreased progressively: from 92.3% of the patients in group A to 72.7% in group B and 58.6% in group C, showing a reversal trend with respect to the musculoskeletal involvement.

The histological class by renal biopsy (performed in 41 patients) paralleled in severity the frequency of renal involvement in the three age classes. Mesangial proliferative nephritis (Class II) was found in only 9% of group A patients, 25% of group B and 59% of group C. Conversely, a more severe renal involvement, frequently leading to end-stage renal failure and grouped into the Classes III and IV, was found in 64% of iSLE patients, 63% of those of group B and 36% of group C.

Neurological involvement was present in 6 patients (46.2%) from group A and included seizures, encephalopathy with brain calcification (2), subarachnoid hemorrhage (1) and developmental delay (2). Two patients (18.2%) in group B and 6 (20.7%) in group C had neurological manifestations, including severe headaches (2), diplopia (1), peripheral neuropathy (1), extrapyramidal symptoms (1), hallucinations and behavioural changes (1), significant EEG abnormalities (5) and cerebral hemorrhage (1). Although neurological involvement was more frequent and severe in group A, the difference between the three groups did not reach statistical significance ($P = 0.217$).

The cumulative disease activity at diagnosis, as measured by the SLEDAI, was significantly higher in iSLE than in the other two age groups (Figure 1). This confirms that the disease severity is inversely related with the age at onset.

Laboratory features

Anemia and thrombocytopenia were more frequent in iSLE than in the other two groups (Table 1). In particular, these two abnormalities were observed in three-quarters of the patients of this group. Thrombocytopenia was found in one third of teenagers and rarely observed in prepubertal patients. Leukopenia, reported in one-third of our postpubertal patients, was rarely reported both in prepubertal and iSLE.

Complement fractions C3 and C4 were reduced in more than 50% of the patients, with no significant difference among the age groups. Similarly, no statistical differences between the groups were found in the frequency of ANA, anti-dsDNA, aCL and LAC.

Outcome

Adequate follow-up information was not available for all children in group A. However, the overall prognosis in this group was significantly worse than in the other two groups, despite a shorter length of follow-up (average 94.2 months for group B, 95.8 months for group C versus 36.7 months for group A). Five infants died 2 to 31 months after the disease onset for infections (2), multiorgan failure (1), congestive heart failure (1) and pulmonary hemorrhage (1). Only one death occurred in group C, 24 months after disease onset, due to sepsis. The survival rate in group A was 69.5% at 1 year and 61.5% at 5 years. In contrast, the survival rate for group B was 100% at 1 and 5 years, and for postpubertal patients it was 100% at 1 year and 96% at 5 years.

Discussion

Several studies on pSLE suggest that age at onset modifies the expression of the disease in terms of clinical presentation, pattern of organ involvement and serological findings.[21–25]

In the present study we analysed if SLE has different clinical features in three specific age classes, i.e. infantile, prepubertal and postpubertal characterized respectively, by partial immaturity of the immune system, absence and presence of hormonal influence.

One important difference between the three classes is the gender distribution. In postpubertal patients the female preponderance is quite evident, with F : M ratio 5.4 times higher than in prepubertal children. This underlines the significant role played by sex hormones in the disease pathogenesis in the group of older patients, whereas in younger patients a combination of immature immunological status and infections may have a more important role. The higher frequency of positive family history for autoimmune diseases in the infantile SLE group, compared with the other two (46.2% versus 25% and 28.6%, respectively), may suggest an increased genetic predisposition to develop SLE in younger patients. This finding, already previously reported[5] should be kept in mind, in this group of patients, in order to rule out congenital immunodeficiencies such as complement fractions [26,27] or IgA deficiencies.[28]

Age at onset seems to affect both clinical manifestations and prognosis of pSLE.[23,24,29] SLE that begins in childhood tends to be more severe, with frequent cardiac, pulmonary and renal involvement and is

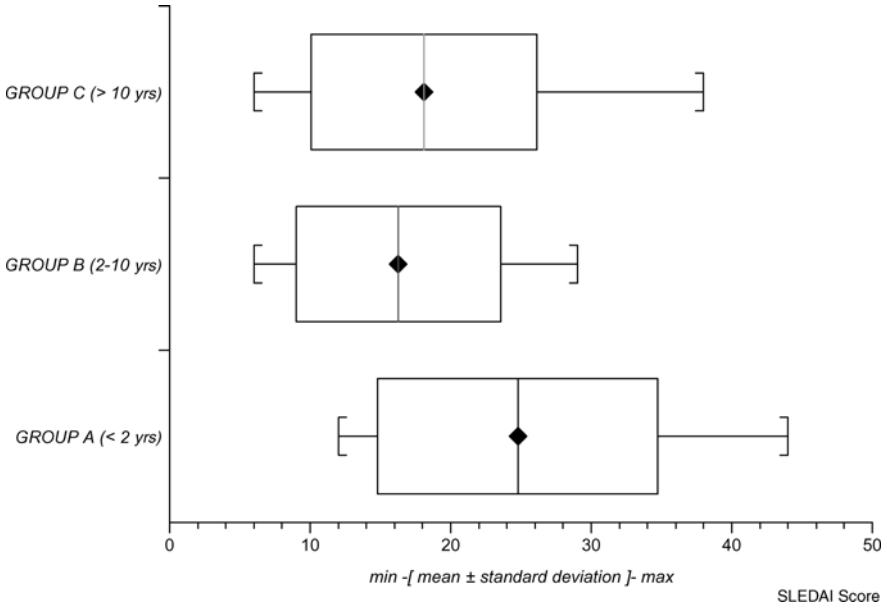

Figure 1 SLEDAI score at diagnosis in the three pediatric SLE age classes.

associated with a more aggressive course than in the following ages. In particular, in this study the onset of the disease was more acute in infantile SLE (group A), and the disease duration at diagnosis was significantly shorter than in the other two groups (mean 0.7 months). In this group the presenting symptoms were quite unspecific and characterized by fever, rash, irritability or by bleeding signs such as petechiae or purpura, but the clinical picture rapidly evolved revealing more specific signs of organ involvement. In the older patients (group B and C) the mean disease duration at diagnosis was 8- to 9-fold higher. This may be partially due to the lesser frequency of acute systemic symptoms and partially by the fact that patients have less serious organ involvement, the main complaints being fatigue, arthritis, alopecia and malar rash.

In the current study we found no significant differences in the incidence of mucocutaneous, lymph node and gastrointestinal involvement among patients of different age groups. From infantile to postpubertal onset we noticed an increasing prevalence of musculoskeletal involvement (from 23% to 76%). Conversely, renal and CNS involvement and hepatosplenomegaly tend to decrease in frequency in older children. In particular, this decrease in frequency was accompanied by a decrease in severity of renal involvement as seen in the renal histology picture analysis. In fact the more severe WHO Classes (III and IV) were found with decreasing frequency starting from 64% in iSLE patients to 36% in postpubertal patients (group C).

Cardiovascular and respiratory involvement, occurred significantly more frequently in iSLE than in the other two groups and were even cause of death in two patients. The SLEDAI, as index of disease activity at onset[10], also clearly confirmed the higher severity of SLE in infants.

To find out if the changes observed in clinical manifestations of the disease in different age classes are also present in adulthood, we combined the results of our study with those of a recent French publication analysing two different adult age classes[30]. Although with the limits of a comparison of different ethnic populations and of possible referral bias, we summarized the trend of the frequency of six organ involvements in five different age classes from infancy to old age (Figure 2).

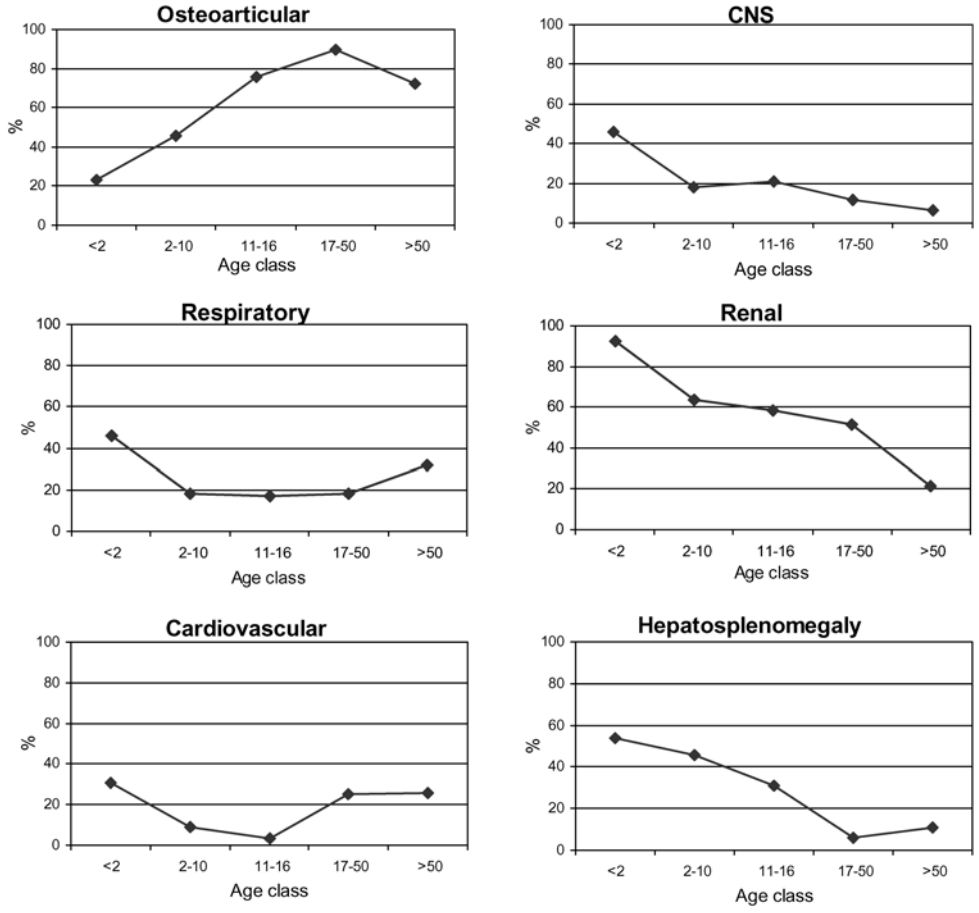

Figure 2 Frequency of organ involvement, at SLE diagnosis in different age groups.

In general, the musculoskeletal involvement increases with age reaching a prevalence of over 80% in adulthood and old age. Conversely, hepatosplenomegaly, neurological and renal involvement progressively decrease from childhood to adulthood. Respiratory and cardiovascular symptoms seem to follow a bimodal trend with higher frequency in infants and elderly patients and lower in the intermediate age classes. Although quite interesting, we did not find a reasonable explanation for these findings, but a combination of physiological changes in the immune and hormonal systems might play a role.

As for outcome, we observed a worse survival in infant and prepubertal SLE patients. This finding, already observed by other authors, underlines that the immaturity or the presence of mild defects of the immune system may play a role in disease severity, and maybe in drug resistance as well.

Conclusions

The prevalence of internal organ involvement in pSLE seems to decrease with the age. Infantile SLE is more severe, and mortality is higher than in the following ages. Postpubertal patients have a strong female preponderance and more specific signs of disease at onset. Prepubertal patients have an intermediate disease severity and no gender predilection.

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