

Original article

A comparison of the outcome of adolescent and adult-onset systemic lupus erythematosus

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Abstract

Objective. Previous reports have suggested that juvenile-onset SLE is associated with a worse prognosis than adult-onset disease. There have been limited studies in adolescents. We sought to assess the effect of adolescent-onset SLE on the clinical course of a large multi-ethnic cohort.

Methods. Patients consisted of individuals diagnosed with SLE between 11 and 18 years of age in a tertiary referral centre. All patients with adult-onset disease were used as controls. Data were analysed by univariable and multivariable analysis for demographic, clinical and serological data.

Results. One hundred and twenty-four patients with adolescent-onset and 484 patients with adult-onset disease were identified. There was a higher percentage of males (12.9% vs 7.2%; $P=0.036$) and patients of Asian ethnicity within the adolescent group ($P<0.01$). By univariable analysis, adolescent-onset SLE was associated with more frequent LN and haemolytic anaemia and less serositis and SS. Ischaemic vascular events occurred in 32 adult-onset patients (6.6%) and 3 adolescent-onset patients (2.4%; $P=0.08$). Thirty-five adult-onset patients developed cancer (6.8%) compared with five of the adolescent-onset group (4.8%; $P=0.54$). The standardized mortality rate was significantly increased in females with adolescent-onset SLE (14.4; 95% CI 4.44, 24.4) compared with patients with adult-onset SLE. By multivariable analysis, adolescent-onset SLE retained a significant association with LN.

Conclusion. Adolescent-onset SLE is associated with a significantly increased risk of LN and, importantly, with a marked increase in mortality. These data suggest a more aggressive phenotype of disease in patients with onset of SLE in adolescence and supports the need for intensive follow-up and intensive therapy in this population.

Key words: systemic lupus erythematosus, paediatric/juvenile rheumatology, outcome measures, adolescent rheumatology.

Introduction

SLE is a chronic, multisystem autoimmune disorder with a highly variable presentation and course [1–10]. Its prevalence is notably higher in individuals of Afro-Caribbean extraction and in females of childbearing age [1, 4]; this

gender predilection is present but less pronounced in the paediatric population [4, 6]. The course of the disease is characterized by periods of remission and relapse [2, 4, 9–11] and the clinical manifestations may range from skin rashes and oral ulcers to life-threatening renal and neurological disease [1, 2, 6, 8, 12, 13].

SLE is diagnosed early in life (before age 16) in up to 20% of cases [11, 14–18]. However, epidemiological studies specifically focused on adolescents are rare and diagnosis in adolescence is not always obvious since the clinical and serological features (e.g. positive ANA) commonly seen in SLE may mimic other medical conditions frequently observed in adolescents, such as infectious diseases [4, 7, 14–17].

Some studies have reported that the manifestations of juvenile-onset SLE are similar to those found in adult-onset disease, admitting that the defining difference

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between these two groups is the age of onset [6, 19]. Nevertheless, it is now accepted that age at disease onset does have a relevant impact on the clinical course and outcome [11, 20]. It has been established that juvenile-onset SLE tends to have a more aggressive presentation and course, with high rates of organ involvement and increased need for long-term immunosuppressive medications [19–21]. These observations are important, as they are likely to cause an increased risk of cumulative damage and consequently early morbidity and mortality in the juvenile-onset group [6, 7, 18, 20–23]. LN, one of the most devastating SLE features, has been reported to be more prevalent in juvenile-onset SLE, with an earlier diagnosis associated with a poor prognosis [15, 19]. Other relevant outcomes, such as the presence of cardiovascular disease, demonstrate no apparent association with juvenile-onset disease [4]. Despite a dramatic improvement in mortality in both adult- and adolescent-onset disease in the last few decades, owing largely to significant advances in the therapy of SLE, patients diagnosed with SLE at an early age remain at high risk for early mortality in their young adult years [1, 18, 20].

To date, few clinical, immunological and serological differences have been found and confirmed between juvenile- and adult-onset SLE and specific data referring to adolescent-onset SLE are lacking. The objectives of this study were to compare a multi-ethnic cohort of patients with adolescent- or adult-onset SLE followed up in the same academic centre [University College Hospital London (UCH)] for the pattern of organ involvement, serological profile and outcomes (i.e. mortality, development of LN, cardiovascular disease and the diagnosis of cancer).

Patients and methods

Patients

The study population consisted of 608 patients with SLE followed in the Centre for Rheumatology at UCH from January 1979 to April 2012. All patients fulfilled the revised ACR criteria for lupus (1982, further revised 1997). Adolescent-onset disease was defined as diagnosis (age at the time of fulfilment of the fourth ACR criterion) between 11 and 18 years of age, while those diagnosed at ≥ 19 years were classified as adult-onset disease. Of the study cohort, approximately one-third of patients were local to the catchment area of UCH, one-third were from the greater London area and one-third were referred from other locations within the UK. This descriptive study involved assessment of data collected routinely at the time of clinical follow-up. No additional clinical samples or outpatient attendances are required from patients under follow-up within our cohort for study purposes, thus ethical approval and informed consent were not required.

Collection of clinical and serological information

The demographic details recorded included gender, age at diagnosis, ethnicity and duration of follow-up.

Information on the clinical manifestations and serological profile of each patient was identified by review of hospital records and questionnaires completed at the time of each attendance at the outpatient department. These questionnaires are based on the BILAG index and have been completed at each assessment for >20 years, representing a wealth of clinical information. Each item is then coded as present or absent for the purposes of this analysis. In reality, the BILAG system also distinguishes present features into better/worse/same compared to 1 month ago. The data are presented as the cumulative clinical manifestations throughout the follow-up period and serological data at the time of diagnosis. Additional information in relation to cardiovascular morbidity, cancer occurrence and mortality was obtained from additional locally maintained databases.

The specific clinical manifestations recorded for this analysis were rash, photosensitivity, alopecia, arthritis, oral ulcers, serositis, nephritis, CNS involvement, haematological dyscrasia (leucopenia, lymphopenia, thrombocytopenia, haemolytic anaemia) and SS. The standard ACR definitions for the former manifestations were employed. Additionally, SS was defined as keratoconjunctivitis sicca with confirmation by either a positive Schirmer's test or characteristic Rose Bengal staining or xerostomia confirmed by positive labial biopsy, sialometry or typical changes in salivary scintigraphy. With particular reference to LN, $>95\%$ of patients had biopsy-proven disease. The remaining patients had clinically overt disease in combination with either elevated 24-h urinary protein excretion, elevated protein:creatinine ratio, hypertension or an active urinary sediment.

The serological variables assessed included ANA measured by IIF with a Hep-2 substrate. A titre of $\geq 1:80$ was considered positive. Other autoantibodies assessed were RF, measured by both latex testing and RA particle agglutination (RAPA) assay techniques (positive titre $\geq 1:80$); antibodies to ENA, which included Sm, Ro, La and RNP, measured by ELISA; and anti-ds DNA, measured by ELISA (Shield Diagnostics, Dundee, UK) and IF with *Crithidia* luciferase as the substrate. The patient was regarded as anti-dsDNA positive if the *Crithidia* test was positive or if the ELISA result was at least twice the upper limit of normal (normal <50 U/l) on two occasions. Complement component C3 was measured by laser nephelometry.

Statistical analysis

All statistical analyses were carried out using SPSS 20 statistical software (IBM, Armonk, NY, USA). Demographic details are reported as percentages or the median and interquartile range (IQR). For the comparison of continuous variables a Mann-Whitney *U* test was employed, while for categorical data a chi-squared or Fisher's exact test, where appropriate, was used. A *P*-value <0.05 was considered a statistically significant effect. The Bonferroni correction was applied to adjust for the effect of multiple comparisons. In order to take into account the different ethnic and gender distribution

TABLE 1 Demographic details

	Adult-onset SLE	Adolescent-onset SLE
Age at onset, median (IQR), years	31 (25–39)	15 (13–17)*
Gender, female, %	92.8	87.1*
Duration of follow-up, median (IQR), years	16 (9–24)	14 (9–20)
Ethnicity, %		
Caucasian	64.5	50.8
Afro-Caribbean	21.9	21
Asian	13.4	28.2*

* $P < 0.05$.

of the study cohorts, multivariable regression was used to determine the effect of age category at onset on the outcome of interest. In order to further ascertain the impact of age of onset on mortality and to take into account the varying length of follow-up we calculated the standardized mortality rate (SMR) for each cohort using age- and gender-specific mortality data for the UK (England) population. This information was generated by comparing the observed number of events over the follow-up period with the expected number of deaths using the general population data as the reference, for which 95% CIs were generated to ascertain the statistical significance of the result. A similar approach was used to determine a standardized cancer incidence using age-specific (in 5-year age bands) national information on cancer incidence.

Results

A total of 608 patients meeting the ACR criteria for SLE were identified. Of these, 484 were classified as adult-onset disease; 124 patients were diagnosed between 11 and 18 years of age, comprising the adolescent cohort. Of the 608 patients included in the study, only 25 were lost to follow-up, the majority of whom had moved overseas. The baseline demographics are outlined in Table 1. As has previously been reported, the female:male ratio was significantly lower in the adolescent-onset cohort (6.75% vs 12.82% in the adult-onset group), albeit somewhat higher than previously reported. This finding may reflect the inclusion of other groups of patients diagnosed ≤ 10 years and possibly reflects the emerging influence of hormones on the female predilection for SLE from teenage years onwards.

There was also a significant discrepancy in the ethnicity profile of the groups. While Caucasians accounted for the majority of patients in both (64.5% adult onset, 50.8% adolescent onset), there was a greater preponderance of Asian patients within the adolescent group (13.4% adult onset, 28.2% adolescent onset, $P = 0.001$). Both groups had a similar duration of follow-up, with a median follow-up of 16 years (IQR 9–24) in the adult-onset patients and

TABLE 2 Cumulative clinical manifestations

	Adult-onset SLE, %	Adolescent-onset SLE, %	P-value
Rash	65.6	67.5	0.75
Photosensitivity	40.8	38.5	0.68
Alopecia	22.5	22.6	1.00
Oral ulcers	25	29	0.359
Musculoskeletal	92.8	88.7	0.14
Serositis	41.4	28.2	0.007*
Nephritis	27.1	42.7	0.001*
CNS	20.8	22.6	0.712
SS	9.9	2.4	0.006*
Haemolytic anaemia	2.9	7.3	0.035*
Leucopenia	29.7	29.8	1.00
Lymphopenia	75.7	72.7	0.56
Thrombocytopenia	14.8	18.0	0.40

*Indicates significant results.

14 years (IQR 9–20) in the adolescent-onset cohort ($P = 0.097$).

Cumulative clinical manifestations

The frequencies of the observed cumulative clinical manifestations are summarized in Table 2. The prevalence of LN was significantly higher within the adolescent cohort, affecting 42.7% of patients with adolescent-onset disease and 27.1% of adult-onset patients ($P = 0.001$). Histological analysis of renal biopsy specimens was available in 96% of patients with LN and demonstrated no significant difference between groups. Class IV nephritis was the most common grade in both cohorts. The relative distribution of histological subclasses is summarized in Table 3.

Haemolytic anaemia was also more commonly observed in those with adolescent-onset disease (7.3% vs 2.9%, $P = 0.035$). Adult-onset patients were found to have significantly more prevalent serositis (41.4% vs 28.2% of adolescents, $P = 0.007$) and sicca symptoms (9.9% vs 2.4%, $P = 0.006$) than those with adolescent-onset SLE. After adjustment for the effect of multiple comparisons only a significantly higher prevalence of LN retained statistical significance. This relationship was also preserved after logistic regression to take into account gender and ethnicity. Although a trend towards lower serum complement was observed in the adolescent cohort, no significant serological differences were noted between the groups (Table 4).

The effect of age category at onset on the occurrence of important outcomes, in particular cardiovascular disease, cancer and mortality, was examined. By univariable analysis, there was a non-significant trend towards a higher prevalence of a significant vascular event [myocardial infarction or cerebrovascular accident (MI or CVA)] in those with adult-onset disease, with a rate of 6.6% observed compared with 2.4% in the adolescent cohort ($P = 0.084$). This translated into a cumulative event rate of 32 per 4182 years follow-up in the adult-onset cohort

TABLE 3 Histological subclasses of LN

	Adult onset SLE, %	Adolescent-onset SLE, %
Grade 1	1.7	4
Grade 2	7.8	10.2
Grade 3	21.7	24.5
Grade 4	47.8	40.8
Grade 5	20	20.4
Grade 6	0.9	0

The relative percentage of each subclass of LN diagnosed on biopsy is reported. No significant difference between the groups in the distribution of LN grades was observed.

TABLE 4 Serological profile of study cohort

	Adult-onset SLE, %	Adolescent-onset SLE, %	P-value
ANA	99.2	97.6	0.16
RF	26.2	18.7	0.136
Anti-Sm	15	18.2	0.402
Anti-RNP	28.1	29.2	0.8
Anti-Ro	38	33.3	0.398
Anti-La	14.6	11.7	0.47
Anti-ds DNA	61.4	67.8	0.21
Low C3	44.2	54	0.055

Results are reported as a percentage of the total population.

compared with three events per 1828 years follow-up in the adolescent-onset cohort. The majority of events were myocardial infarctions representing 62.8% of events (CVA 31.4% and PVD 5.7%). All subjects in the adolescent-onset group were female ($n=3$), while 84% of the adult-onset cohort who suffered from a vascular event were female.

Similarly the diagnosis of cancer was not significantly different between study groups. Forty-one cases of cancer were observed in 40 patients. This resulted in a rate of 7.2% in adult-onset patients and 4% in adolescent-onset SLE ($P=0.2$). There were a variety of primary lesions, but the overall numbers were too small to allow a between-groups comparison of cancer distribution. The median age at cancer diagnosis in the adult-onset group was 53 (IQR 38–61) and 46 (IQR 27–50) in the adolescent group (P =not significant). In order to take into account differences in the follow-up periods and age at cancer diagnosis we determined an age-standardized cancer incidence. Interestingly, neither patients with adult-onset or adolescent-onset disease had a significantly increased incidence of cancer compared with the general population. There was a trend towards a higher incidence of cancer in patients with adolescent-onset disease, with a standardized incidence rate of 4.55 (95% CI 0.56, 8.54), compared with that of adult-onset disease (1.2, 95% CI 0.805, 1.6).

Over the median follow-up of 16 years in the adult-onset group and 14 years in the adolescent cohort, a mortality rate of 15.7% (75 cases) and 6.5% (8 cases), respectively, was observed, indicating a significantly higher mortality within the adult-onset category ($P=0.008$). The median age at death for the adult-onset group was 49 years (IQR 38–61 years) and 21.5 years (17.5–26.5 years) in the adolescent-onset group. While the cause of death was similarly distributed between vascular events, cancer, infection, renal failure and other causes in the adult cohort, 62.5% of deaths in the adolescent-onset cohort were due to infection. This was further investigated by calculating the SMR of adolescent-onset and adult-onset disease using age- and gender-specific information for the UK population as a reference. Interestingly, females with adolescent-onset SLE had a greatly increased SMR of 14.42 (95% CI 4.44–24.4) in comparison to the background population, albeit with a broad CI owing to the sample size. Results of the same analysis for males and females with adult-onset disease were 2.45 (95% CI 0.63–4.27) and 3.42 (95% CI 2.61–4.23) respectively, indicating increased mortality rates in comparison to the background population, though not to the extent of females with adolescent-onset disease. It was not possible to generate a relevant SMR for males with adolescent-onset disease owing to the small number of subjects within this group.

It should be highlighted that the lack of a significant difference between groups in the occurrence of cardiovascular events/cancer may still be clinically relevant given the comparative youth of the patients in the adolescent-onset cohort. Thus, this cohort apparently lacks the traditionally reported protective effect of youth on the occurrence of these two disease-related outcomes

Discussion

This is a retrospective study whose results support the hypothesis that SLE, when diagnosed in adolescence, may be associated with serious organ damage and have a worse prognosis than adult-onset disease. On review of the literature, we found only one analogous study assessing outcomes in adolescent-onset SLE, a much smaller study of 31 patients with adolescent-onset disease. [14] Nonetheless, they also identified a significantly higher prevalence of renal and CNS disease in their cohort in comparison to the adult-onset comparator group. Other groups have, in their study of early onset-SLE, defined juvenile onset differently (from 1 to a maximum age ranging from 14 to 18 years). Thus, data on the clinical presentation and outcome measures in adolescents are notably lacking and may differ from a general paediatric cohort given the hormonal changes occurring at this time.

Analysing the epidemiological data of our study, the cohort of patients was mainly females. The percentage of females was significantly higher in adult-onset SLE patients in comparison with the adolescent-onset group, in keeping with the well-described female predominance in adult series and a higher percentage of males when the diagnosis is accomplished in childhood [17]. Clinically, adolescent-onset disease was associated with more

frequent nephritis and haemolytic anaemia, while adult patients demonstrated more prevalent serositis and sicca symptoms. No significant difference in the prevalence of CNS disease was found, in contrast with the previously reported study on adolescent disease. The immunological markers assayed included the determination of complement C3 (decreased value) and the presence of ANA, RF, anti-Sm, anti-RNP, anti-Ro, anti-La and/or anti-dsDNA antibodies. There were no distinguishing serological markers between groups, although the percentage of patients with a decreased C3 value was increased in adolescents (54% vs 44%), $P=0.055$.

LN is an indicator of adverse prognosis. In our cohort, renal disease was significantly more common in adolescent-onset disease. The higher prevalence in this group reinforces the concept that adolescent-onset SLE is associated with a worse outcome. Previous studies reported that nephritis occurs in 30–80% of childhood patients with SLE (more frequently than in adult-onset) and, in most cases, is evident early in the course of disease. However, it still remains controversial if nephritis diagnosed in adult-onset SLE is associated with a better prognosis [6]. From previous studies, the 5-year renal survival rates of childhood-onset LN ranged from 44 to 93%, depending on ethnicity, patient selection and the initial severity of renal disease [24]. In a multi-centre analysis of 714 adult-onset SLE vs 4700 juvenile-onset SLE patients, it was demonstrated that the rate of renal failure was not significantly lower in adult-onset group, although renal disease and nephrotic syndrome were less common in that group [24].

The other prognostic factors considered in our study were cardiovascular disease and cancer. In patients with SLE, atherosclerosis occurs early in the course of the disease and has an accelerated course [25]. Patients with SLE have a higher number of traditional risk factors compared with controls, but it has been clearly shown that these risk factors cannot fully explain the presence of atherosclerosis in patients with SLE [25]. In our study, not unexpectedly, the occurrence of cardiovascular events in adult-onset SLE was increased, compared to adolescent-onset, but the result was not statistically significant ($P > 0.05$). This finding strongly suggests that, even though less susceptible, adolescent patients were not protected against vascular events despite their youth. This lack of protection also applies to cancer, which, in previous studies, has been shown to have a slightly higher incidence in SLE patients than in the general population [26]. Many authors have suggested that it might be due to the use of immunosuppressant therapy especially if taken for a long period of time [25]. Non-Hodgkin's lymphoma (3–4 × higher than normal population), cervical cancer as well as bronchial carcinomas are the most frequently described malignancies in the literature, but other primary locations may also be found [20, 26]. Despite an expected higher prevalence of cancer in adult-onset SLE, no difference between the analysed groups in this study (6.8% in adults vs 4.8% in adolescents) was found. To take into account the demographic (notably age) differences and

varying follow-up in our study cohort, we generated a standardized cancer incidence from UK national data. We noted a trend towards a higher cancer incidence in comparison to the general population in adolescent-onset patients. However, the 95% CI was broad due to the low number of observed events and thus did not achieve statistical significance. This finding does, however, indicate a need for a larger scale study on this particular outcome in patients diagnosed with SLE in childhood. The most frequent primary lesions observed in our study were breast cancer (8), lung cancer (5) and Hodgkin's lymphoma (4) out of 40 patients with cancer diagnosis.

Finally, the assessment of mortality demonstrated that, during follow-up, 80 patients within our cohort died, 75 (15.7%) in the adult-onset group and 8 (6.5%) in those with adolescent-onset SLE. Our expectations had been that young patients would be less susceptible to premature death than they actually were. This is demonstrated by the marked increase in SMR in females with adolescent-onset disease, a group with an SMR of 14.4 times that of an age-matched general population. There is a relative paucity of information in relation to SMRs in juvenile SLE and clearly this is an area that needs to be further explored. In particular, information from a larger cohort will help to more accurately define the magnitude of this risk and perhaps contribute further to an understanding of the causes of the elevated risk in this vulnerable cohort.

The main limitations of our study were the lack of complete information concerning the treatment of some patients and the broad range of the follow-up period. In relation to the latter point, however, the average follow-up for each group was similar and did not result in a statistically significant difference between groups. Additionally, in relation to both mortality and cancer, the addition of SMR and standardized incidence data takes into account the variability in follow-up periods between cohorts as well as compensating for those lost to follow-up. As this is a large tertiary referral centre, there is the potential for selection bias, with patients with more aggressive disease referred for expertise in management. This clearly applies to both the adult and adolescent cohorts, and our findings support those from previous reports. Finally, it should be highlighted that adolescent patients, as a group, present a number of additional challenges in relation to the approach to management. Akin to what has been observed in other chronic conditions in adolescence, compliance with therapy in SLE can be a significant issue with the potential to contribute to adverse outcomes. These issues and the additional psychological stress that can accompany the diagnosis of a chronic illness at a potentially vulnerable time mean that a more holistic approach to management is required for adolescent patients.

In conclusion, while in adults a predominance of clinical features such as serositis and sicca symptoms was observed, in adolescents the disease was significantly more associated with the development of LN, which is considered an indicator of a worse prognosis. A notable percentage of adolescent-onset patients also developed cardiovascular events or cancer, which are uncommon

diseases in young patients. While the observed mortality rate was significantly greater in adult-onset SLE, eight deaths were reported in the younger group, more than expected in a cohort of 124 patients. Because of recent improvements in life expectancy in SLE, susceptibility to the accumulation of co-morbidities is increased with a higher frequency of chronic complications, such as cardiovascular and renal disease, as well as malignancy. Given the paucity of information specific to adolescent-onset disease, it is uncertain whether the findings from this cohort are generalizable to juvenile-onset SLE as a whole. Theoretically, hormonal changes during puberty resulting in immune perturbation might be a contributing factor to increased disease activity and adverse outcome in adolescent disease, therefore we propose that further studies focused on adolescents with SLE are necessary to inform us fully about the clinical phenotype and long-term outcome of this subgroup.

Rheumatology key messages

- Adolescent-onset SLE has an adverse prognosis, particularly with an increased incidence of LN.
- The onset of SLE in adolescence carries with it a significant increase in mortality.

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