Pediatric rheumatology

Disease duration, hypertension and medication requirements are associated with organ damage in childhood-onset systemic lupus erythematosus

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ABSTRACT

Objective

To investigate the frequency of organ damage in childhood-onset systemic lupus erythematosus (SLE) and to identify disease variables and patient characteristics related to organ damage.

Methods

A cohort of 71 patients was examined in a cross-sectional study after a mean disease duration of 10.8 ±8.2 years (mean age 26.4 ±9.8 years). The occurrence of organ damage was measured by the Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index (SDI). Factors analysed as possible explanatory variables of organ damage were the following: demographic variables, clinical variables at diagnosis and during disease course, as well as medication use. Growth and self-reported health status were also measured.

Results

The most frequent areas of organ damage were in the neuropsychiatric (28%), renal (13%) and musculoskeletal (13%) organ systems. Forty-three patients (61%) had evidence of damage. The mean SDI score was 1.3 for the whole study population. Hypertension, longer disease duration and use of cyclophosphamide were factors significantly related to an increasing SDI score in multiple linear regression analyses. Furthermore, patients with damage (SDI ≥ 1) compared to those without damage (SDI = 0) had a significantly higher cumulative corticosteroid dose (24.7 g versus 10.6 g) and more frequently required high-dose prednisolone at diagnosis (68% versus 43%).

Conclusion

Evidence of organ damage was found in 61% of all patients. Long disease duration, known hypertension and use of cylophosphamide were significantly associated with an increasing SDI score. Furthermore high-dose prednisolone at diagnosis and cumulative prednisolone dose were significantly related to the presence of organ damage.

Key words

Systemic lupus erythematosus, outcome assessment, paediatrics, children.

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Introduction

Systemic lupus erythematosus (SLE) is a multisystem, inflammatory autoimmune disease with a variable course and prognosis. The incidence of SLE in children under 15 years of age is about 10 times lower compared to those in adult (1). The long-term prognosis for children with SLE has improved considerably over the last four decades, with 10-year survival rates now exceeding 85% (2-4). The increase in survival has been attributed to earlier diagnoses of patients with milder disease, more aggressive treatment in early disease and improved management of severe disease (including renal dialysis and transplantation) (5, 6).

As a result of improved life expectancy, other morbidity in SLE patients is increasing. These patients now suffer from a range of complications from the disease itself or side effects of its treatment (e.g. cerebrovascular accidents, cataracts, renal failure, hypertension, osteoporosis, avascular necrosis) (7). The assessment of outcome in childhood-onset SLE should therefore take account of the morbidity and disease complications, of which there are few studies in the literature. Most previous studies of paediatric SLE have focused on describing clinical manifestations and serology (8-10), and have used survival as an indicator of outcome (2,11-14).

The Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index (SDI) is a validated instrument, which is developed to measure non reversible organ damage in adults with SLE (15, 16). This instrument is designed to assess organ damage in SLE since onset of the disease and it is newly evaluated for its usefulness in children (17). A number of factors have been linked to damage in childhood-onset SLE (17-19), some of these are medication use, cumulative disease activity, disease duration and certain clinical manifestations at diagnosis like neuropsychiatric disease. The impact of any risk factor alone or in combination with other factors on observed damage in childhood-onset SLE is unclear.

The purpose of this study was to examine the occurrence of organ damage in a Norwegian childhood-onset SLE cohort and to identify disease variables and patient characteristics related to organ damage, as assessed by the SDI.

Patients and methods

Patients

The current cross-sectional study was performed at the Department of Rheumatology, Rikshospitalet University Hospital, which serves the majority of the population of southern Norway, i.e. approximately 2.5 million people (20). The study population comprised 71 children, adolescents and young adults (92%) out of 77 patients identified with childhood-onset SLE in Norway between January 1980 and June 2003 by the search strategy described below.

Sixty-four patients were identified from the Rikshospitalet's patient register, who had been admitted to Rikshospitalet between January 1980 and June 2003. Fifty-nine of these patients could be contacted and were included in the study, the other 5 patients were not enrolled because one had a history of drug-induced lupus and 4 had died. No significant differences were found between deceased patients and those alive with respect to age, sex, disease duration and disease activity at diagnosis (data not shown).

Thirteen patients, who had not been admitted to the Rikshospitalet, were identified from other hospitals. Five of them were recruited from the National Register of Autoimmune Disease, which was established in 1998. Eight patients were reported from the northern and western regions of Norway as a reply to questionnaires about new and previously treated childhood-onset SLE patients mailed to all paediatric and rheumatology clinics in Norway in the years 2000 and 2001. Seven of these patients were enrolled and one patient chose not to participate.

No significant differences were found between patients recruited from the Rikshospitalet compared to those included from other hospitals with respect to age, sex, disease duration, disease activity, hypertension and medication requirements. The patients recruited from the Rikshospitalet probably

represent the vast majority of patients diagnosed with childhood-onset SLE in southern Norway in the given time period, since our department represents the only paediatric rheumatology clinic in southern Norway. In addition, the aforementioned questionnaires did not report on any new patients from southern Norway, and those reported were already registered at our hospital's patient register.

The inclusion criteria were: disease onset within the age of 16 years, minimum disease duration 12 months, and the presence of at least four American Rheumatism Association Criteria for classification of systemic lupus erythematosus (ARA criteria) (21).

Informed consent was obtained from the patients and/or parents. The study was approved by the Regional Ethics Committee for Medical Research.

Data collection and instruments

All the patients were examined during a one-day programme at Rikshospitalet, which included a clinical examination by a single physician (VL), laboratory tests and self-reported health status questionnaires. Disease activity was assessed by the SLE Disease Activity Index (SLEDAI) (22) and organ damage was measured by the SDI (15). In addition retrospective SLEDAI scores were assigned for the time of diagnosis and SDI scores were assigned retrospectively for 1, 5 and 10 years' disease duration for patients with at least 10 years disease duration.

Data required to assign the scores retrospectively were available from the patient's medical records for all patients. Data were obtained by contacting the relevant local hospital for those patients who had not previously been admitted to Rikshospitalet and for those who were no longer being followed up regularly at Rikshospitalet. Furthermore disease damage was assessed by Physician's global assessment of damage on a 5-point Likert scale (1 = no evidence, 2 = mild, 3 = moderate, 4 = severe and 5 = very severe damage) by the same physician, independently from the SDI score by including all information on disease activity, laboratory analyses, disease course and disability (23).

Information on clinical manifestations at disease onset and during disease, laboratory data, medication and other factors possibly related to organ damage were obtained from the patient's histories and medical records. "Hypertension ever" was defined as hypertension requiring antihypertensive medication. Disease onset was defined as the time of appearance of the initial clinical symptoms clearly attributable to SLE. Disease duration was defined as the period from diagnosis until the time of the study.

SLEDAI

The SLEDAI is a validated disease-specific index for measuring disease activity in SLE patients, and was first developed for use in adults (22). The instrument has later been validated for use in patients with childhood-onset SLE (24). The index consists of 24 weighted attributes grouped into 9 organ systems, including clinical and laboratory measures of SLE disease activity. The SLEDAI records new or recurrent disease activity during a 10-day period prior to the assessment and has a theoretically possible range of 0 to 105, with 0 being no disease activity.

SDI

This index is a validated instrument that quantifies non-reversible organ damage that has occurred since the onset of disease (15), and has recently been found to have face, content and construct validity when used in childhood-onset SLE (17). Both disease-specific and non-disease-specific damage is included in the index. Therefore damage can be caused by inflammation from the disease, medication side effects or other comorbid conditions, but must be present continuously for at least 6 months. Damage is defined for 12 organ systems: ocular (range 0-2), neuropsychiatric (0-6), renal (0-3), pulmonary (0-5), cardiovascular (0-6), peripheral vascular (0-5), gastrointestinal (0-6), musculoskeletal (0-7), skin (0-3), gonadal (0-1), endocrine damage (0-1) and malignancy (0-2). A score of 0 is assigned to patients with no non-reversible damage and the maximum possible score is 47 (25). The item cognitive impairment was scored only if patients had clearly poor concentration, difficulties in spoken language and if memory deficits were apparently evident or reported by parents or family members. Premature gonadal failure was only scored if patients previously had regularly menses, and subsequent developed secondary amenorrhoea.

Growth

The patients' current height was measured by a wall-mounted Harpenden stadiometer. Data on parents' height were obtained from the patients or directly from the parents. Predicted final height was calculated using the following formula: (maternal height + paternal height + 13 cm)/2 for boys and (maternal height + paternal height -13 cm)/2 for girls (26). For patients less than 18 years old the estimated final height was determined by extrapolating the current height to maturity (27), using growth curves based on national standards. Standard deviations of mean final height for Norwegian adults were used to calculate whether patients were within ±1 or 2 SD of the predicted final height (28).

Corticosteroid use

Data were obtained from the medical records on cumulative corticosteroid dose including pulses with methylprednisolone (expressed as prednisolone equivalents) and the number of months of corticosteroid treatment. The dose of methylprednisolone in milligrams was multiplied by 1.25 to convert the amount to prednisolone equivalents. High-dose prednisolone at time of diagnosis was defined as treatment with prednisolone dose ≥ 20 mg or ≥ 1 mg/kg/day. The overall documentation of corticosteroid use in the records was good and often detailed. If relevant time periods were not documented the lowest possible cumulative dose was calculated.

CHAQ/HAQ

Physical disability was measured with the CHAQ (Childhood Health Assessment Questionnaire) and for patients older than 18 years with the HAQ

(Health Assessment Questionnaire). The CHAQ/HAQ measures physical function in eight areas: dressing and grooming, arising, eating, walking, hygiene, reaching, gripping and other activities. Disability is scored from 0 to 3, where 0 means no difficulty with the daily activities and 3 means unable to perform activities (29-31). The CHAQ has been validated for use in various rheumatic diseases, although not for childhood-onset SLE (32). However, the HAQ, which is the equivalent instrument in adults, has been found valid in adult SLE patients (30).

SF-36

The 36-item Short-Form Health Survey (SF-36) was chosen to measure psychosocial functioning, since this instrument is applicable to a wide range of age like in our cohort, and secondly to have a single measure for the patients assessed. This questionnaire can be applied to patients 14 years or more. Only three of the patients in our cohort were aged less than 14 years and these were not asked to fill out the form. It is unlikely that these few patients could have made a significant difference in our results. The SF-36 is a generic validated health questionnaire that measures eight health dimensions: physical functioning (10 items), role limitations due to physical problems (4 items), bodily pain (2 items), vitality/energy/fatigue (4 items), social functioning (2 items), general mental health (5 items), and a one-item measure of reported health transition (33). The SF-36 scales were scored according to published scoring procedures, each expressed in values from 0 to 100, with the higher value representing better function/health. The questionnaire has been translated and culturally adapted for use by Norwegians (34, 35).

Statistical analysis

Differences between patient groups were tested by independent sample t-test for continuous normally distributed variables, Mann-Whitney test for continuous non-normally distributed variables, and chi-square test or Fisher's exact test for categorical variables. Multiple linear regression analyses were used to investigate the relationship between potential explanatory variables and the SDI score. Patient and disease characteristics were assumed to be explanatory variables. Eighteen possible variables were at first examined by univariate analysis and included in the multiple models if P was less than 0.2. If independent variables were highly intercorrelated ($r>0.7$), only one of two variables could be chosen for the multivariate analysis. The number of independent variables in the multiple model was restricted to the square root of the sample size (36), the variables were entered by forward variable selection procedures. We thoroughly checked for possible violations from the model assumptions during analyses. For all analyses, P-values less than or equal to 0.05 were considered significant. All statistical analyses were performed by the SPSS version 11.0.

Results

Patients

The 71 childhood-onset SLE patients had a mean disease duration of 10.8 years (± SD 8.2) and mean age 26.4 years (± SD 9.8, range 9.8 – 49.3) at examination. The majority of the patients (93%) were Caucasians. Among the non-white patients the ethnicity was as followed: 3 were Asian, 1 Hispanic and one black. Fifty-four (76%) patients were female and 17 male (24%), giving a male:female ratio of 1: 3.2. Patient characteristics and disease variables are shown in Table I. The most frequent clinical symptoms at diagnosis were malar rash (55%), photosensitivity (55%), arthritis (48%), fever (45%) and renal disorder (25%) (data not shown). These clinical manifestations continued to be the most frequent symptoms during the course of disease, and at time of examination 31 patients (44%) had acquired renal disorder.

Organ damage

The mean SDI score was 1.3 ± SD 1.7 for the total study group. Forty-three patients (61%) had a damage-score ≥ 1, which means having evidence of non-reversible damage. Among these patients the following damage scores were assigned: 25 patients had a score of 1, 9 patients had a score of 2 or 3, 6 patients had a score of 4 or 5, and 3 patient had a score of 6 or 7.

Organ damage occurred most frequently in the neuropsychiatric (28%), renal (13%) and musculoskeletal (13%) organ systems, as shown in Table II. In the neuropsychiatric domain, cognitive impairment (13%) and cerebrovascular accidents (10%) accounted for most of the scores. The frequency of neuropsychiatric damage still remained high (23%), when excluding the item score cognitive impairment. Cerebral strokes were partly accounted for by 2 patients with antiphospholipid-syndrome. Renal impairment occurred in 9 patients, and required transplantation in 4 of them. Muscle atrophy and osteoporosis with fracture or vertebral collapse accounted for most of the scores in the musculoskeletal system.

Comparison of the damage accrued over time in specific organ systems as assessed in patients with at least 10 years' disease duration (n = 35), showed that the highest increase in organ damage occurred in the neuropsychiatric organ system. The percentage of patients with damage in the neuropsychiatric system increased from 3% to 14% and 20% after 1, 5 and 10 years disease duration, respectively. In contrast, damage in other organ systems increased from 0-3% to 0-9% and 0-12% after a disease duration of 1, 5 and 10 years, respectively. Patients with less than 10 years' disease duration showed no significant difference in SLEDAI at diagnosis or as regards the requirement for high dose prednisolone at diagnosis and immunosuppressive therapies compared with those with more than 10 years' disease duration (data not shown).

For the assessment of growth failure data on parents' height were available from 58 patients. Most patients (76%) were within 1 SD of their predicted height. Eleven patients (19%) were below 1 SD of the mean predicted height and 5% were above 1 SD. The proportion of patients below 2 SD below the mean was 10% of the total group.

The survival during the mean follow-up of 11 years of the 63 patients identified from the Rikshospitalet's patient register was 93.6%. The 4 patients who

died had a higher SDI score at last examination than those who were alive (3.3 versus 1.3, *P* value 0.012).

Comparison of patients with damage versus patients with no evidence of damage

Twenty-eight patients (39%) had a SDI score=0, meaning they had no damage. Patients with SDI score ≥ 1 had on average more frequently required high-dose prednisolone at diagnosis and had a higher cumulative steroid dose, longer duration of treatment with corticosteroids and a higher frequency of hypertension than those with no damage (*P* values ranged from 0.003 to 0.023). Disease activity, disease duration and frequency of renal or neurological disease at diagnosis showed higher values in patients with a damage-score ≥ 1, but this was not statistically significant (data not shown).

The CHAQ/HAQ was higher and the SF-36 scores were lower in the patient group with organ damage, indicating that they had poorer health, but this was not statistically significant (data not shown). The mean CHAQ/HAQ was 0.4, with 35 patients (49%) having scores >0 and 11 patients (16%) having scores ≥ 1.

Factors associated with increasing organ damage

To identify the most important demographic and disease-related factors associated to organ damage a multiple linear regression analysis was performed (Table III). In univariate analysis disease duration, SLEDAI at diagnosis and current, renal disease, known hypertension, use of cyclophosphamide ever, cumulative prednisolone dose, duration of treatment with prednisolone and requirement of high-dose prednisolone at diagnosis showed significant association with SDI. In multiple linear regression analyses only disease duration, hypertension and use of cyclophosphamide ever were identified as factors significantly associated with increasing SDI score. Forward and backward stepwise regression showed similar results. The final model explained 44% of the variance in the damage scores.

Table I. Characteristics of 71 childhood-onset SLE patients.

Variable	SLE patients		
	No. (%)	Mean (SD)	Median
Females	54 (76)		
Caucasian	66 (93)		
Age at current examination, years		26.4 (9.8)	26.5
Disease duration, years		10.8 (8.2)	9.8
Age at diagnosis, years		15.3 (4.8)	14.5
Age at symptom onset, years		12.5 (2.9)	13.0
SLEDAI at diagnosis		10.5 (8.3)	9.0
SLEDAI at current examination		3.1 (4.0)	2.0
ESR at diagnosis, mm/hour		56.1 (37.5)	50.0
SDI		1.3 (1.7)	1.0
SDI ≥ 1	43 (61)		
Hypertension ever	15 (21)		
Antinuclear antibodies*	66 (93)		
Anti dsDNA*	51 (72)		
Corticosteroids			
Ever users	66 (93)		
Current users	43 (61)		
Mean current dose among users		8.0 (7.5)	5.0
Cumulative dose, g		19.1 (24.5)	8.5
Duration, months		68.7 (84.3)	36.0
High-dose at diagnosis†	41 (61)		
Mean high-dose at diagnosis among users†, (mg/day)		46.8 (22.3)	45.0
Antimalarials, current users	32 (45)		
Azathioprine, current users	20 (28)		
Cyclophosphamide, current users	8 (11)		
Cyclophosphamide ever users	23 (32)		

*At any time during disease; † Prednisolone dose ≥ 20 mg/day or ≥ 1 mg/kg/day.
SLEDAI: SLE Disease Activity Index, SDI: Systemic Lupus International Collaborative Clinics/American College of Rheumatology Damage Index, ESR: erythrocyte sedimentation rate.

Discussion

The frequency of organ damage in childhood-onset SLE as assessed by the SDI and the relationship between possible risk factors and organ damage, were evaluated in the present cohort of 71 childhood-onset SLE patients after a mean disease duration of 10.8 years. Forty-three patients (61%) had evidence of non-reversible damage (SDI score ≥ 1) with an average SDI score for the total study group of 1.3 (SD ± 1.7). We found that a longer disease duration, known hypertension and the use ever of cyclophosphamide were factors significantly associated with an increasing SDI score. Other disease variables significantly related to the presence of damage were the cumulative prednisolone dose and high-dose prednisolone at diagnosis. To our knowledge, this is the first study to describe long-term organ damage in Scandinavian patients with childhood-onset SLE.

It is known that organ damage accrues gradually over time (37). Despite the long disease duration, the mean SDI score in our patients was lower compared with two previous paediatric SLE studies (17, 38), which reported a mean SDI of 1.8 and 2.0 after a disease duration of 3.3 and 7.2 years, respectively. In contrast to these, when comparing with a recently published multicenter study in childhood-onset SLE (18) which found a mean SDI of 1.1 after 5.7 years, the mean SDI in our patients was higher.

Our results may have been influenced by the high proportion of Caucasian patients (93%) in our study cohort in contrast to others (6, 13, 17, 18). Caucasians have previously been found to

Table II. Systemic Lupus International Collaborative Clinics/American College of Rheumatology Damage Index (SDI) scores for 71 childhood onset SLE patients.

Domain, item	no.	(%)	Domain, item	no.	(%)
1. Ocular	3	(4)	6. Peripheral vascular	6	(9)
Any cataract ever	2	(3)	Claudication for 6 months	2	(3)
Retinal change or optic atrophy	2	(3)	Minor tissue loss ever (e.g. pulp space)	2	(3)
			Significant tissue loss ever (e.g. loss of digit or limb)	0	(0)
2. Neuropsychiatric	20	(28)	Venous thrombosis with swelling, ulceration OR venous stasis	3	(4)
Cognitive impairment or major pychosis	9	(13)			
Seizures requring therapy for 6 months	4	(6)			
Cerebrovascular accident ever	7	(10)	6. Gastrointestinal	3	(4)
Cranial or peripheral neuropathy	3	(4)	Infarction or resection of bowel below duodenum, spleen, liver or gall bladder ever	1	(1)
Tranverse myelitis	0	(0)			
			Mesenteric insufficiency	0	(0)
3. Renal	9	(13)	Chronic peritonitis	0	(0)
Estimated or measured glomerular filtration <50%	1	(1)	Stricture or upper gastrointestinal surgery ever	2	(3)
Proteinuria ≥3.5 gm/24 hours or	4	(6)	Pancreatic insuffiency requiring enzyme replacement or with pseudocyst	0	(0)
End-stage renal disease (regardless of dialysis or transplantation)	4	(6)			
			7. Musculoskeletal	9	(13)
			Muscle atrophy or weakness	8	(11)
4. Pulmonary	3	(4)	Deforming or erosive arthritis	2	(3)
Pulmonal hypertension	1	(1)	Osteoporosis with fracture or vertebral collapse	4	(6)
Pulmonary fibrosis	1	(1)	Avascular necrosis	3	(4)
Shrinking lung	1	(1)	Osteomyelitis	0	(0)
Pleural fibrosis	0	(0)	Ruptured tendon	0	(0)
Pulmonary infarction or resection not for malignancy	0	(0)			
			8. Skin	2	(3)
			Scarring chronic alopecia	2	(3)
5. Cardiovascular	4	(6)	Extensive scarring or panniculum other than scalp and pulp space	0	(0)
Angina or coronary artery bypass	2	(3)			
Myocardial infarction ever	2	(3)	Skin ulceration	0	(0)
Cardiomyopathy	0	(0)			
Valvular disease	3	(4)	9. Premature gonadal failure	3	(4)
Pericarditis for 6 months or Pericardiectomy	0	(0)			
			10. Diabetes (regardless of treatment)	1	(1)
			11. Malignancy (exclude dysplasia)	1	(1)

have a more favourable prognosis than non-Caucasians (39, 40). A British study has reported significantly lower SDI scores after 10 years' disease duration in adult Caucasian SLE patients compared with Afro-Caribbean and Asian patients (1.15 versus 2.55 and 2.57, respectively) (16). The reason for the poorer prognosis in black SLE patients is not known, although disease outcome may be influenced by socioeconomic factors and genetics-related ethnic factors (41-43). However, the influence of ethnicity in childhood-onset SLE is controversial (38, 39). On the other hand, our results may reflect a high proportion of patients with mild lupus disease, due to the free access to health care for children in Norway and universal public health care coverage. This may lead to the earlier recognition of mild disease and the earlier institution of adequate and more aggressive treatment, which may prevent the development of severe manifestations. However, it is difficult to compare the findings of different paediatric SLE studies due to the influence of patient selection; for example, the high SDI score found by Mietunen *et al*. was partly accounted for by the high scores in deceased patients (38), whereas deceased patients were not included in our study.

The most common areas of damage noted in our childhood-onset SLE cohort were in the neuropsychiatric (28%), renal (13%) and musculoskeletal (13%) organ systems, findings that corroborate those of other studies of both childhood-onset SLE (17) and adult-onset SLE (44). Although the frequencies of renal and musculoskeletal damage were in the lower range in our study, this may also be explained in terms of ethnicity (39) and mild disease, like the total SDI score.

In contrast, the frequency of damage in the neuropsychiatric organ system was higher in our patients (28%) than in those of other paediatric SLE studies, where frequencies of 11% and 16% after 3.3 and 5.7 years, respectively, were found (17, 18). The two commonest types of neuropsychiatric damage in our patient cohort were cognitive impairment (13%) and cerebrovascular accidents (10%). The slope of the accrual of organ damage differs for each organ system (37, 45). In our study, damage in the neuropsychiatric organ system showed the highest increase over time compared with damage in other organ systems. Although the reason for the high frequency of damage in the neuropsychiatric organ system in our patients is not known, it seems to be related to the varying pattern of damage accrual in the specific organ sys-

tems.

Growth failure is important in pediatric SLE (23) and it has been suggested that it should be included in the SDI for children. The proportion of patients with short stature (2 SD below the mean predicted height) was 10% in our study, which is comparable to the findings of Ravelli *et al*. (18), who reported a frequency of 16% of patients with growth failure. In addition, it has been commented that the SDI for use in childhood-onset SLE could benefit from other modifications as well (46). This includes a clearer definition of cognitive impairment in paediatric SLE patients, a weight-based definition of proteinuria, and assessment of pubertal delay. Likewise, the item of premature gonadal failure based on secondary amenorrhea alone may require modification, as irregular menses form a part of normal body maturation in adolescents.

Factors associated with increasing organ damage identified by multiple regression analysis in our study were longer disease duration, hypertension and use of cyclophosphamide ever. Ravelli *et al.* (18) also reported cyclophosphamide pulses and disease duration to be significantly related to evidence of organ damage. The observed association between cyclophosphamide exposure and evidence of damage may reflect the fact that cyclophosphamide is often given to patients with severe, life-threatening disease, and that a high proportion of these patients have organ damage. Although specific side effects of the medication may be another explanation, this is less likely because the reported side effects of cyclophosphamide, apart from malignancies and premature gonadal failure, are not measured by the SDI. However, it has been found by Brunner *et al*. that immunosuppresive agents probably protect against disease damage (17). Long disease duration as a factor associated with organ damage has previously been described in adult SLE (43, 47, 48) and the adverse prognostic effect of hypertension has been reported in childhood-onset SLE (13).

Cumulative disease activity over time has been found by Brunner *et al*. to be an important risk factor for damage (17). Although we found that SLEDAI at diagnosis was significantly associated with SDI in univariate regression analysis, this factor was not statistically significant in the multiple model. However, it might be a possible limitation of the study that we did not control for cumulative disease activity. Other risk factors that have previously been linked with a poor outcome are young age at diagnosis (13), male sex (49, 50), neuropsychiatric manifestations at diagnosis (ARA-criteria) (18, 19), the presence of antiphospholipid antibodies (17), and acute thrombocytopaenia (17, 40). Our study did not confirm the hypothesis that the presence of antiphospholipid antibodies or neuropsychiatric manifestation at diagnosis are risk factors for damage, in the latter case probably because of the low patient sample size (n= 2) fullfilling these ARA criteria (seizures and psychosis) at diagnosis.

We found the cumulative prednisolone dose and use of high-dose prednisolone at diagnosis to be significantly associated with SDI ≥ 1 when we compared patients with and without damage. Both factors have been reported to be important risk factors for damage in paedi-

Table III. Patient characteristics and disease variables predicting the SDI score by multiple linear regression analysis in 71 childhood-onset SLE patients.

	Univariate analysis		
Variable	Beta¶	95% CI	P
Sex (female =1, male =2)	-0.308	-1.251, 0.635	0.517
Age, yrs	0.024	-0.016, 0.064	0.232
Disease duration, yrs	0.063	0.014, 0.107	0.012
Age at disease onset, yrs	-0.073	-0.213, 0.066	0.298
Age at diagnosis, yrs	-0.049	-0.131, 0.034	0.245
SLEDAI at diagnosis	0.057	0.009, 0.105	0.020
SLEDAI current	0.031	-0.070, 0.131	0.543
Renal disease at diagnosis§*	0.713	-0.192, 1.619	0.121
Neurologic disease at diagnosis§*	-0.323	-2.750, 2.104	0.791
Anti ds DNA at diagnosis*	0.447	-0.399, 1.293	0.295
No. of ARA-criteria at diagnosis	-0.089	-0.369, 0.191	0.528
ESR at diagnosis, mm/hour	0.010	-0.001, 0.022	0.078
Presence of antiphospholipid antibodies*	-0.494	-2.093, 1.104	0.537
Hypertension ever*	1.333	0.400, 2.267	0.006
Cyclophosphamide ever*	1.242	0.437, 2.046	0.003
Prednisolone, cumulative dose, g	0.026	0.010, 0.041	0.002
Prednisolone duration, months	0.009	0.005, 0.013	< 0.001
High-dose prednisolone at diagnosis*	1.186	0.348, 2.023	0.006
	Multiple linear regression analysis#		
Variable	Beta¶	95% CI	P
Cyclophosphamide ever*	1.538	0.658, 2.418	0.001
Hypertension ever*	1.266	0.266, 2.266	0.014
Disease duration, yrs	0.059	0.012, 0.106	0.015
SLEDAI at diagnosis	-	-	-
Renal disease at diagnosis§*	-	-	-
ESR diagnosis, mm/hour	-	-	-
Prednisolone, cumulative dose, g	-	-	-
High-dose prednisolone at diagnosis*	-	-	-
R^2 (%)		44	

* (no = 0, yes = 1).

§ According to the American Rheumatism Association Criteria for the classification of systemic lupus erythematosus.

¶ Beta values are unstandardised coefficients.

Final model identifying significant predictors of SDI, R^2: total explained variance of the model, SLEDAI: SLE Disease Activity Index, ESR: erythrocyte sedimentation rate.

atric SLE (17), and corticosteroids are also known to contribute to the development of damage in adult SLE (44, 45). Furthermore, group comparison of patients with damage to those without showed no significant difference in the measures of physical and mental health status.

A drawbacks of our study might be the limited sample size, which means that all multivariate analyses must be regarded as generating hypotheses that need further testing. The SLE patients in the present study had a high mean age and long disease duration. The long disease duration may be a strength of this study, since damage accumulates over time. Another strength of our study is that all the patients identified from the patient registers and who were alive could be contacted and were willing to participate. Clinical manifestations at disease onset and during the course of disease were comparable to those in other studies (8-10), indicating that the cohort was representative for patients with childhood-onset SLE. The ratio of female to male children (1: 3.2) in our cohort was similar to those in two previous studies (38, 39). The reason for the higher proportion of males in childhood-onset SLE compared to adult-onset SLE is unknown, but it may be partly influenced by hormonal factors.

In conclusion, in the present study 61% of the childhood-onset SLE patients had evidence of organ damage after a mean disease duration of 10.8 years, as measured by the SDI. Factors significantly associated with increased organ damage were longer disease duration, hypertension and use of cyclophosphamide ever. The observed association between cyclophosphamide and organ damage may reflect the fact that patients with severe disease have a higher proportion of organ damage, as this medication in general is given to patients with severe, life-threatening disease. Thus, it does not mean that cyclophosphamide is the primary cause of damage. The clinical implications of our findings may increase the clinicians' awareness of which patients are at risk of organ damage, which is important for its prevention and treatment.

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