Influence of age at disease onset in the outcome of paediatric systemic lupus erythematosus

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Objectives. The aim of this study was to investigate the influence of age at disease onset in the outcome of paediatric SLE (pSLE).
Methods. Fifty-six patients with pSLE, divided into three groups (pre-pubertal, peripubertal and post-pubertal onset), were studied. The SDI (SLICC/ACR Damage Index for SLE), patients' characteristics, disease manifestations and treatments were compared using Fisher's exact test and Kruskal–Wallis test. Kaplan–Meier curves were constructed to compare the risk of damage occurrence.
Results. The risk of damage (SDI $\geqslant 1$) significantly decreased when age at disease onset increased (89% in pre-pubertal pSLE, 57% in peripubertal pSLE and 38% in post-pubertal pSLE). This excess of risk was found in all disease duration intervals studied (1–3, 3–5, 5–8, 8–10, >10 years) and at the end of follow-up. Kaplan–Meier curves indicated a higher and earlier risk of damage in younger patients. Young children showed higher frequency of autoimmune family history. The frequency of neuropsychiatric disorders and damages decreased with age at disease onset ($P < 0.05$). Cumulative duration of high-dose prednisone (> 0.5 mg/kg/day) and number of immunosuppressive drugs used that seem to contribute to damage significantly increased when age at disease onset decreased.
Conclusions. The risk of damage is inversely correlated with age at disease onset in pSLE. The poorer outcome observed in younger children may be explained by a more severe disease expression, may be a higher infectious susceptibility, and a more aggressive therapy, particularly within the first 6 months of disease course.

KEY WORDS: Systemic lupus erythematosus, Paediatric, Age, Damage, Treatment, Prognosis, Outcome.

Introduction

SLE is a multisystem inflammatory autoimmune disease that usually affects young women, with 10–17% of cases occurring in childhood [1–8]. Several studies suggest that both clinical and biological features of SLE are influenced by age at disease onset, and that SLE may be more severe in childhood onset than in adulthood onset [1–5, 8–13].

As mortality decreased remarkably over the last few decades [14, 15] probably secondary to better recognition and therapeutic approaches, children and adolescents with paediatric-onset SLE (pSLE) are now faced with considerable morbidity due to sequelae of disease activity, side effects of medications and co-morbid conditions [12, 13, 16–19]. Risk factors of poor prognosis have been reported in pSLE, such as male sex [3, 20–23] and non-Caucasian origin [1, 22, 24], although data are controversial [9, 25]. Several authors found a significant correlation between damage and the presence of aPLs [12, 19, 26], some manifestations like acute thrombocytopenia [12], neuropsychiatric symptoms [16], hypertension especially in patients with diffuse proliferative glomerulonephritis [1, 9, 17] and cumulative disease activity [12, 18].

In adults with SLE, increasing age and longer disease duration have been associated with damage [27–30]. However, the influence of age at disease onset in pSLE prognosis remains unclear [9, 12, 15, 16, 18, 23, 31]. The primary objective of this study was to investigate the relationship between outcome and age at disease onset in pSLE. To assess the difference of outcome severity, three groups were compared according to age at disease onset (pre-pubertal, peripubertal or post-pubertal onset).

Methods

Study design and patient selection

Medical charts of all patients followed for SLE at the University Hospital of Lyon (France) in paediatric consultation and/or hospitalization units between 1996 and 2006 or in internal medicine, nephrology, rheumatology, dermatology and cardiology units between 2000 and 2006 were reviewed. The inclusion criteria were: (i) onset of SLE symptoms $\leqslant 16$ years of age, (ii) at least 4 of 11 classification criteria for SLE [32] and (iii) disease duration $\geqslant 12$ months (except for fatal cases). This cohort of patients has already been studied [19] and was followed up regularly until June 2006. The study was approved by the local ethics committee (The Committee of Protection of the Persons of the Hospices Civils of Lyon). Patients were divided into three groups based on age at disease onset: the pre-pubertal group included boys of age $\leqslant 9$ years and girls $\leqslant 8$ years, the peripubertal group included boys of age >9 and <14 years and girls >8 and <13 years and the post-pubertal group included boys of age $\geqslant 14$ years and girls $\geqslant 13$ years. The clinical and laboratory characteristics of each group, their treatment and outcome were compared.

Data collection

All data collected from medical charts were recorded on a standardized data form. The following parameters have been considered for each patient: age at disease onset (first symptoms related to SLE), sex, ethnicity, positive family history for autoimmune disease (in first- and second-degree relatives), clinical and laboratory characteristics during the first month and during follow-up, disease duration, treatment and outcome. Clinical manifestations and results of laboratory tests were monitored every month or every 3 months when disease was active and every 6 months or 12 months when disease was quiescent.

ANAs were determined by IIF and anti-dsDNA antibodies by IIF using *Crithidia luciliae* as substrate and by Farr test. Each patient had a mean of 6.9 ± 3.3 (median 6) determinations of aPLs. The aPL detection was performed at least twice except in one patient (one aPL-negative sample) who died of pulmonary embolism secondary to anti-thrombin III deficit, 2 months after

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pSLE onset. In the aPL-positive group, as previously described [19], we distinguished transient aPL [positive detection once or several times, but not confirmed (negative) at 6–12 weeks of interval], intermittent aPL [positive detection at least twice and confirmed at 6–12 weeks of interval, with period(s) of negative detection] and persistent aPL (positive detection at least twice and confirmed at 6–12 weeks of interval, without any period of negative detection). LAC was detected using international recommendations [33], and aCLs were measured by commercial (BioRad–Sanofi Pasteur) or in-house immunoenzymatic assay (ELISA). Threshold detection was >12 UMPL and >24 UGPL for aCL, IgM and IgG, respectively, for samples collected from 2000 to 2006, and >11 UMPL and >23 UGPL for aCL, IgM and IgG, respectively, for samples collected before 2000. Anti-β2 glycoprotein I was not considered as these aPLs were not regularly detected.

In order to evaluate the severity of pSLE outcome, we considered the value of SDI (SLICC/ACR Damage Index or SLICC/ACR for SLE). The SDI score measures the accumulated and irreversible damage that result from both disease activity and adverse effects of medications. This score, ranging from 0 to 47 (41 items), includes the assessment of 12 organ systems [34, 35]. To eliminate the effects of disease duration that were shown to correlate with damage accumulation [16, 17], the SDI score was assessed at regular time intervals: 1–3, 3–5, 5–8, 8–10, >10 years and at the end of follow-up. The delay of occurrence and the type of damage were recorded for each patient. We also considered the mortality rate and causes of death. The main outcome parameter was the risk of damage (SDI $\geqslant$1) or death related to pSLE.

Statistical analysis

All data were analysed using R software (R Development Core Team) version 2.6.0. Results were expressed as mean $\pm$ S.D. and medians for continuous variables, and as numbers (percentages) for binary and categorical variables. Patients with pre-pubertal, peripubertal and post-pubertal pSLE onset were compared using the Fisher's exact test for categorical variables and the Kruskal–Wallis test for continuous variables. To compare the delay of damage occurrence according to age at disease onset, time-to-damage end points were plotted using life table method, and Kaplan–Meier curves were compared by log rank test. *P*-values <0.05 were considered significant.

Results

Fifty-six patients with pSLE were included in this study: 39 girls (70%) and 17 boys (30%). The mean age at pSLE onset was 12.6 $\pm$ 3.2 years (median 13 years). Nine children (16%) developed the first symptoms of pSLE before puberty onset, 21 (38%) during the peripubertal period and 26 (46%) during the post-pubertal period. Sex ratio and ethnicity were not significantly different between the three age groups at disease onset (Table 1). Although the values did not reach statistical significance, a positive family history for autoimmune disease (particularly SLE) was more frequently reported in patients with pre- and peripubertal disease onset than in patients with post-pubertal onset. The risk of damage (SDI $\geqslant$1) in pSLE was high (30/56, 54%) and significantly decreased with age at disease onset (89% in the pre-pubertal group, 57% in the peripubertal group and 38% in the post-pubertal group). The disease duration was not statistically significant in the three groups (mean 6.6–8 years).

Clinical and biological features in patients with pre-, peri- and post-pubertal pSLE onset

Disease manifestations among the three age groups of pSLE onset were different during the first month of disease and during follow-up (Fig. 1). The initial presentation of pSLE frequently involved haematological and renal organ systems in children with pre-pubertal disease onset. During the follow-up, the frequency of neuropsychiatric involvement (epilepsy, cerebral vasculitis and cerebrovascular accident in particular) increased when age at disease onset decreased ($P = 0.037$). The frequency of ANAs (100%), anti-dsDNA antibodies (88–95%) and aPLs (50–62%) were comparable in the three groups. Different types of aPLs (LAC and aCL) were often associated (16/56, 29%), but aCLs (27/56, 48%) were more frequent than LACs (20/56, 36%). The frequency of persistent and intermittent aPL was roughly similar in the three groups, whereas transient aPLs were significantly more frequent in peripubertal pSLE (62%) than in pre- (0%) or post-pubertal pSLE (15%). Ten patients (18%) developed APS (three in the pre-pubertal group, one in the peripubertal group and six in the post-pubertal group, $P = 0.09$). The risk of thrombosis (most frequently venous) was high in the three groups (44, 24 and 35% in the pre-, peri- and post-pubertal groups, respectively), but no statistical difference was seen.

Severe infections were reported in 16 (29%) patients (12 septicaemia, 11 pneumonia, 2 pyelonephritis, 2 myositis, 1 meningitis) implicating bacteria (in particular *Staphylococcus aureus*, 14 cases) rather than other microorganisms (*Myxovirus influenzae* and *Cryptococcus neoformans*, one case each). All infected patients had received corticosteroids or another immunosuppressive treatment. The frequency of infectious complications was higher in younger patients, although not significantly so (44, 38 and 15% in pre-, peri- and post-pubertal pSLE, respectively).

TABLE 1. Characteristics and outcome of 56 patients with pSLE according to age at disease onset

	Pre-pubertal onset $n = 9$ (16%)	Peripubertal onset $n = 21$ (38%)	Post-pubertal onset $n = 26$ (46%)	P^a
Age at disease onset, years				
Girls	$\leqslant$8	>8 and <13	$\geqslant$13	
Boys	$\leqslant$9	>9 and <14	$\geqslant$14	
Mean (median) range	6.9 (7.4) 3.8–8.9	12.1 (12.3) 9–13.5	15 (15.5) 13–16.8	
Sex ratio (female/male)	2 (6/3)	2 (14/7)	2.7 (19/7)	NS
Ethnicity				
Caucasian	4 (44)	14 (67)	14 (54)	NS
African	4 (44)	3 (14)	5 (19)	NS
Asian	–	–	2 (8)	NS
Middle East	–	1 (5)	–	NS
Unknown	1 (11)	3 (14)	5 (19)	NS
Autoimmune family history	2 (22)	6 (29)	1 (4)	0.048
SLE family history	2 (22)	2 (10)	1 (4)	NS
Disease duration, mean (median) range, years	8 (8) 2–12.2	6.6 (6.3) 1.5–14	8 (5.9) 0.2–26.2	NS
Risk of damage, SDI $\geqslant$1	8 (89)	12 (57)	10 (38)	0.032
Death	2[b] (22)	1[c] (5)	2 (8)	NS

Values are given as *n* (%), unless otherwise mentioned. [a]Differences between pre-, peri- and post-pubertal groups with *P*-value >0.05 were not significant (NS). [b]A third patient with pre-pubertal pSLE died a few months after the end of the study. [c]A girl with peripubertal pSLE committed suicide although SLE was benign and quiescent since >1 year. Her death was not considered in these results.
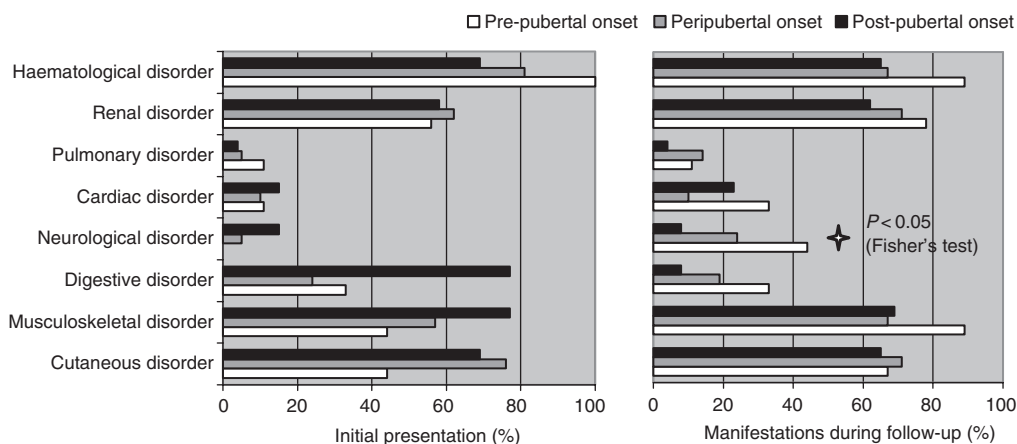
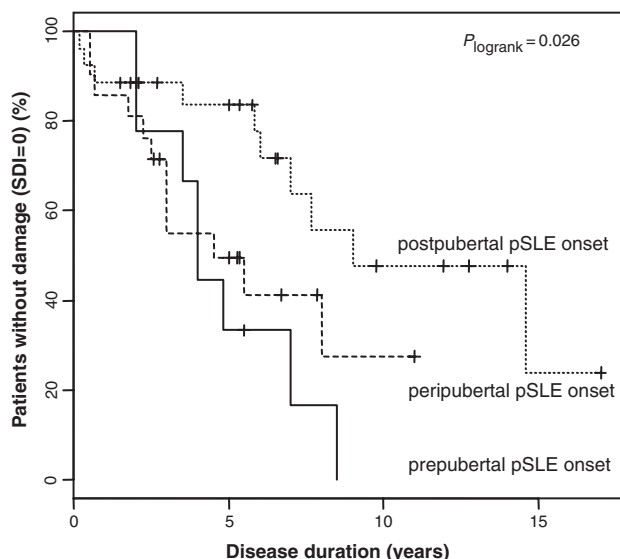FIG. 1. Clinical and biological manifestations in 56 patients with pSLE according to age at disease onset.

FIG. 2. Kaplan–Meier type plot of time to damage occurrence in pSLE according to age at disease onset.

FIG. 3. Risk of damage (SDI $\geqslant$ 1) or death in 56 patients with pSLE according to age at disease onset.

Outcome according to age at disease onset

Most of the children (86%) developed damage within 10 years (62% during the first 5 years, 24% during the next 5 years of disease course). Kaplan–Meier curves showed that the percentage of damage-free patients (SDI = 0) was significantly different between the three groups, decreasing when age at disease onset increased (Fig. 2). The slope of the curves decreased when age at pSLE onset increased as well, suggesting a higher and earlier risk of damage in younger patients. These results indicate that the risk of damage is inversely correlated with age at pSLE onset. The risk of damage (SDI $\geqslant$ 1) or death was calculated at regular time intervals (1–3, 3–5, 5–8, 8–10 and > 10 years) and at the end of follow-up (Fig. 3). We found an excess of risk inversely correlated with age at disease onset in all disease duration intervals.

After a comparable disease duration (mean 6.6–8 years), mean SDI score was 1.3 (range 0–7, median 1). The SDI score decreased with age at disease onset, but not significantly so [mean (median): 1.78 (2), 1.88 (1), 1.08 (0); range 0–4, 0–5 and 0–7 in the pre-, peri- and post-pubertal groups, respectively). Analysis of damage repartition revealed that the most frequent organ systems affected in pSLE were renal (20%), neuropsychiatric (16%),
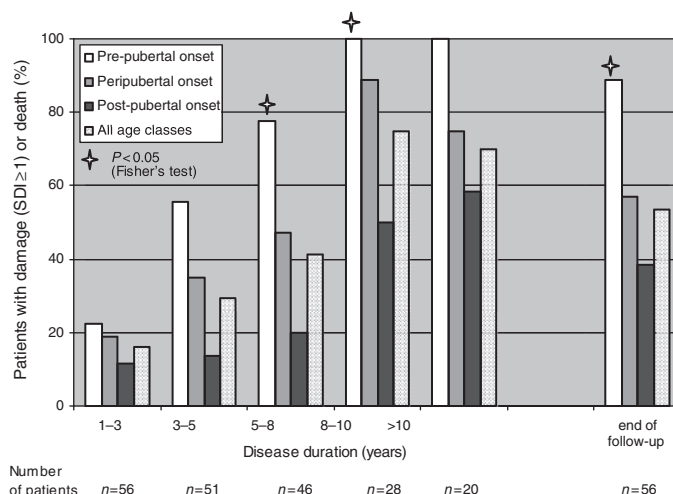
musculoskeletal and skin (13% each) (Table 2). Renal and neuropsychiatric systems were affected early, during the first years of disease course. Although the frequency of renal damage was high but not significantly different between the three groups, the frequency of neuropsychiatric damage was higher in the prepubertal than in the peri- and post-pubertal groups ($P = 0.014$). The frequency of skin and ocular damages decreased with age at disease onset also, even though not significantly ($P = 0.06$ and $P = 0.44$, respectively). All cataracts ($n = 4$) and retinopathies ($n = 2$) occurred in patients treated with corticosteroids ± antimalarials.

Six patients died (11%). In half of the cases, the event took place during the first year after diagnosis. The causes of mortality were often multi-factorial, associating severe SLE flares, infectious complications and thrombotic events in the three age groups [19].

Description of therapies and outcome according to medical treatment

Treatments of patients are summarized in Table 3. The cumulative duration of treatment with high-dose prednisone (> 0.5 mg/kg/day) significantly increased when age at disease onset decreased. Multiple immunosuppressive treatments were successively administered in all patients with pre-pubertal pSLE and more frequently in peripubertal (67%) than in post-pubertal (39%)

TABLE 2. Frequency of damages considered by the SDI in pre-pubertal, peripubertal and post-pubertal pSLE

Damage[a]	All patients (n=56)	Pre-pubertal onset (n=9)	Peripubertal onset (n=21)	Post-pubertal onset (n=26)	P[b]
Ocular	6 (11)	2 (22)	2 (10)	2 (8)	NS
Any cataract	4	1	2	1	
Retinal change	2	1	0	1	
Neuropsychiatric	9 (16)	4 (44)	4 (19)	1 (4)	0.014
Cognitive impairment or major psychosis	3	1	2	0	
Seizures requiring therapy for 6 months	3	2	1	0	
Cerebrovascular accident	3	1	1	1	
Renal	11 (20)	1 (11)	5 (24)	5 (19)	NS
End-stage renal disease	9 (16)	1 (11)	4 (19)	4 (15)	NS
Pulmonary	1 (2)	1 (11)	0 (0)	0 (0)	NS
Pulmonary fibrosis	1	1	0	0	
Cardiovascular	3 (5)	1 (11)	1 (5)	1 (4)	NS
Myocardial infarction	2	1	0	1	
Pericarditis for 6 months	1	0	1	0	
Peripheral vascular	0 (0)	0 (0)	0 (0)	0 (0)	NS
Gastrointestinal	4 (7)	0 (0)	2 (10)	2 (8)	NS
Infarction or resection of bowel, spleen, liver or gall blader	3	0	2	1	
Mesenteric insufficiency	1	0	0	1	
Musculoskeletal	7 (13)	1 (11)	4 (19)	2 (8)	NS
Muscle atrophy or weakness	4	0	4	0	
Deforming or erosive arthritis	1	0	0	1	
Osteoporosis with fracture	2	1	0	1	
Avascular necrosis	3	0	1	2	
Skin	7 (13)	3 (33)	3 (14)	1 (4)	NS
Scarring chronic alopecia	4	3	1	0	
Extensive scarring or panniculum other than scalp and pulpe space	1	0	1	0	
Skin ulceration (excluding thrombosis) for > 6 months	2	0	1	1	
Premature gonadal failure	1 (2)	0 (0)	0 (0)	1 (4)	NS
Diabetes	1 (2)	0 (0)	0 (0)	1 (4)	NS
Malignancy	0 (0)	0 (0)	0 (0)	0 (0)	NS

Values are given as n (%), unless otherwise mentioned. [a]The list of damages presented in this table only comprises the damages developed by the patients included in our study. All the 41 items of the SDI are not listed in this table. [b]Differences between pre-, peri- and post-pubertal groups with P-value > 0.05 were not significant (NS).

TABLE 3. Summary of drug therapies in three age classes of pSLE

Drug therapies	Pre-pubertal onset (n=9)	Peripubertal onset (n=21)	Post-pubertal onset (n=26)	P[a]
Anti-malarial treatment	7 (78)	13 (62)	11 (42)	NS
Corticosteroid treatment	8 (89)	19 (90)	24 (92)	NS
Cumulative duration of corticosteroid therapy, mean (median, range), years	6 (6.3, 0.1–12.2)	5.8 (5.5, 1.5–13)	5.8 (5.3, 0.2–19)	NS
Cumulative duration of high-dose prednisone (> 0.5 mg/kg/day), mean (median, range), months	12.8 (9, 0.2–36)	10.3 (6, 3–36)	5.5 (5.5, 0.2–12)	0.049
Intravenous methylprednisolone pulses (10–30 mg/kg/day)	6 (67)	12 (57)	11 (42)	NS
No. of pulses: mean (median, range)	4.8 (4.5, 2–9)	4.7 (3.5, 2–9)	3.5 (3, 3–6)	NS
Immunosuppressive treatments	6 (67)	12 (57)	18 (69)	NS
Intravenous cyclophosphamide pulses (500–1000 mg/m²)	6 (67)	9 (43)	8 (31)	NS
No. of pulses: mean (median, range)	9.2 (7.5, 6–19)	6.8 (6, 2–13)	7.5 (8.5, 10–14)	NS
Oral cyclophosphamide	1 (11)	2 (10)	1 (4)	NS
AZA	3 (33)	6 (29)	8 (31)	NS
No. of months: mean (median, range)	5.3 (5, 5–6)	18.2 (13, 12–36)	15.6 (6.5, 3.8–76)	0.027
Mycofenolate mofetil	4 (44)	6 (29)	7 (27)	NS
No. of months: mean (median, range)	35.8 (39, 14–51)	12.7 (7, 5–33)	32.4 (25, 3–67)	NS
Cyclosporin	4 (44)	4 (19)	4 (15)	NS
No. of months: mean (median, range)	29.8 (20, 1–78)	11.8 (13.5, 2–18)	27.5 (29, 16–36)	NS
MTX	1 (11)	1 (5)	1 (4)	NS
Multiple immunosuppressive treatments[b]	6 (100)	8 (67)	7 (39)	0.022
No.: mean (median, range)	3 (3, 2–5)	2.2 (2, 1–5)	1.6 (1, 1–4)	0.020
Intravenous immunoglobulins	5 (56)	5 (24)	2 (8)	0.010
Plasma exchanges	1 (11)	3 (14)	2 (8)	NS

Values are given as n (%), unless otherwise mentioned. [a]Differences with P-value > 0.05 were not significant (NS). [b]Two immunosuppressors were successively required in 11 cases, three in 6 cases, and four or five in 2 cases each.

pSLE (P = 0.022). Most of the patients required a successive administration of cyclophosphamide, mycophenolate mofetil and/or AZA. Analysis of initial therapies showed that high-dose prednisone (> 0.5 mg/kg/day) for the first 6 months, intravenous methylprednisolone pulses and/or another immunosuppressive treatment within the first 6 months, were more frequently required when pSLE started during the pre-pubertal period (67%) than during the peripubertal (57%) or the post-pubertal period (23%)

(P = 0.029). Chronic haemodialysis was necessary in nine cases (16%) and renal transplantation in three cases (5%), with no significant difference according to age at disease onset.

We also considered relationships between treatments and risk of damage (SDI ⩾ 1) in pSLE. The occurrence of damage was significantly (P < 0.001) correlated with the use of intravenous methylprednisolone pulses and the cumulative duration of treatment with high-dose prednisone (>0.5 mg/kg/day) but not

with the number of intravenous methylprednisolone pulses and the cumulative duration of corticosteroid therapy (whatever the dose). The use of another immunosuppressive treatment increased the risk of damage ($P = 0.012$), particularly if multiple drugs were associated. The risk of damage was correlated with a longer administration of AZA ($P = 0.049$) but not with the number of cyclophosphamide pulses, or the number of months of mycophenolate mofetil administration.

Discussion

The main objective of this study was to investigate the influence of age at disease onset on the outcome in pSLE. We found that the risk of damage (SDI $\geqslant 1$) significantly decreased when age at disease onset increased (89% in the pre-pubertal group, 57% in the peripubertal group and 38% in the post-pubertal group). This excess of risk, inversely correlated with age at disease onset, was found in all disease duration intervals studied (1–3, 3–5, 5–8, 8–10 and >10 years) and at the end of follow-up. Kaplan–Meier curves confirmed that the risk of damage was inversely correlated with age at pSLE onset, indicating a higher and earlier risk of damage in early-onset disease. Moreover, despite the absence of statistical significance, the SDI score was higher when pSLE began early.

Several studies suggest that SLE tends to be more severe in childhood onset than in adulthood onset [1–5, 8–13]. Children with pSLE were found to have more active disease at presentation and over time, especially active renal disease, more intensive drug therapy and more damage accrual than do adults with SLE [13]. However, the influence of age at disease onset in children remains unclear and has rarely been studied in detail previously. Pluchinotta et al. [36] recently found that the cumulative disease activity at diagnosis as measured by the SLEDAI was significantly higher in infantile ($\leqslant 2$ years) than in pre-pubertal (2–10 years) and post-pubertal (11–16 years) pSLE onset, but long-term evolution was not considered. In a series of 66 patients, Brunner et al. [12] found that age at pSLE diagnosis was not an important predictor of disease damage as measured by the SDI after a short period of follow-up (mean 3.3 ± 2.04, range 0.5–7.9 years). In another study of 57 patients with pSLE, no significant association was observed between age at diagnosis and damage accrual [18] measured using a modified SDI (by adding the item growth failure). The relationship between age at disease onset and death related to pSLE is also controversial [9, 15, 23]. Altogether, our results suggest that the risk of damage is inversely correlated with age at disease onset in pSLE. These findings contrast with those reported in adults for whom increasing age and longer disease duration are correlated with damage [27–30]. Hence, the severity of SLE outcome seems to follow a bimodal trend with higher frequency of damage in younger children and older adults, and lower frequency of damage in intermediate ages.

Given the importance of hormonal factors (e.g. sex hormones) in SLE pathogenesis, age thresholds were defined considering the age at puberty onset. As our study was retrospective and standardized criteria to determine Tanner pubertal stage [37, 38] were not available in all medical charts, the theoretical ages of puberty were considered taking also into account the earlier pubertal development in girls [39–42]. As there are no data permitting to assess the normal age range of pubertal onset in France, like in many countries, the usual ranges of 8–13 years in girls and 9–14 years in boys were used [37, 38]. To strengthen our results, we compared the pre-, peri- and post-pubertal groups using the same age brackets for the two sex ($\leqslant 9$, >9 and <14 and $\geqslant 14$ years, respectively) and the differences observed were roughly similar (data not shown). In particular, the risk of damage was inversely correlated with age at pSLE onset, with robust significance ($P = 0.015$).

In our study, children with pre-pubertal pSLE showed a higher frequency of haematological and renal involvement during the first month, and developed more frequently neuropsychiatric disorders that could lead to disease damage. As reported in another study [36], patients with post-pubertal pSLE presented more specific (e.g. cutaneous and musculoskeletal), like in adults. The peripubertal group had an intermediate presentation. These different patterns of pSLE presentation according to age at disease onset could be explained by genetic, immune and hormonal factors. Patients with early-onset disease may be characterized by a partial immaturity of their immune system and a stronger genetic predisposition to develop pSLE, as suggested in our series by a relatively frequent positive family history for autoimmune disease in younger patients, whereas the influence of sex hormones may play a predominant role in patients with later onset disease.

The main causes of death in SLE (with childhood or adulthood onset) are severe SLE flares, thromboses and infections ($\sim 25\%$ each) [10, 15, 19, 43, 44]. An increasing proportion of death is linked to thromboses [10] and there is a strong association between aPL and thromboses [10, 19, 45–48]. Previously, we found that the risk of thrombosis in pSLE was significantly higher in the presence of aPLs [odds ratio (OR) = 6.42], especially if they persisted over time, and the risk of damage (SDI $\geqslant 1$) was higher in aPL-positive than in aPL-negative patients (OR = 3) [19]. In the present study, the frequency of aPL and thrombosis was high but comparable in the three age groups. The frequency of severe infections, decreasing with age at disease onset, may partially explain the worse survival rate observed in pre-pubertal pSLE [15].

In accordance with other studies, the most frequent organ systems affected in pSLE were renal (20%), neuropsychiatric (16%), musculoskeletal and skin (13% each) [11, 13, 16]. Neuropsychiatric involvement seems to be associated with damage in pSLE [16] and we found that the frequency of neuropsychiatric damage, like the global risk of damage and the SDI value, decreased with age at disease onset. Similar variations of frequency were observed for skin and ocular damages also. There is evidence that some damages (e.g. renal, neuropsychiatric) are more likely to be due to disease activity, as they appear earlier during disease course [12, 18], and that others are more likely to be due to adverse effects of treatments [16–18]. For instance, all ocular damages occurred under corticosteroid and anti-malarial therapies in our series.

The prognostic impact of therapies remains controversial in pSLE [12, 16–18]. In our study, long-term use of high-dose prednisone and successive administration of multiple immunosuppressive agents were correlated with damage. Differences in therapeutic strategies may explain several age-related differences observed in pSLE outcome. We found that the cumulative duration of high-dose prednisone (>0.5 mg/kg/day) and the number of immunosuppressive drugs used significantly increased when age at disease onset decreased although disease duration was comparable in the three age groups. Early intensive therapies were more frequently administered in early-onset disease. Consequently, the poorer outcome observed in children, particularly with early-onset pSLE, is more likely to be linked to adverse effects of intensive therapies than to insufficiently aggressive treatment. Most severe patients had most aggressive therapy but we do not know if the poor outcome in early-disease onset is more likely to be due to adverse effects of treatment, rather than the severe disease itself.

Although the small size of patient groups, particularly the pre-pubertal one, constitutes a limitation of the study, our results suggest that the risk of damage in pSLE is inversely correlated with age at disease onset (pre-pubertal > peripubertal > post-pubertal). The poorer outcome observed in younger children may be explained by a stronger genetic predisposition, a more severe disease expression (e.g. more frequent neuropsychiatric disorders), a higher infectious susceptibility and a more aggressive

therapy, particularly within the first 6 months of disease course. Combined strategies should be considered to improve the prognosis in pSLE, including the rapid control of disease activity (in particular, neuropsychiatric manifestations), the rapid management of infections [50] and thromboses, and the prevention of therapeutic adverse effects.

Rheumatology key messages

- Risk of damage is inversely correlated with age at disease onset in pSLE.
- Frequency of neuropsychiatric disorders, duration of high-dose prednisone and number of immunosuppressors used are higher in younger patients.

Acknowledgements

We are very grateful to all the clinicians and biologists who gave us clinical and biological information.

Disclosure statement: The authors have declared no conflicts of interest.

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