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Clinical features and long-term outcomes of systemic lupus erythematosus: comparative data of childhood, adult and late-onset disease in a national register

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Abstract Systemic lupus erythematosus (SLE) affects predominantly women at reproductive age but may present at any age. Age at disease onset has a modulating effect on presentation and course of disease, but controversies persist regarding its impact on long-term outcome. Our aims were to characterize clinical features, co-morbidities and cumulative damage in childhood-onset, adult-onset and late-onset SLE. Patients with childhood-onset SLE fulfilling ACR 1997 criteria were identified in a nationwide register-Reuma.pt/SLE ($N = 89$) and compared with adult-onset and late-onset counterparts matched 1:1:1 for disease duration. 267 SLE patients with mean disease duration of 11.9 ± 9.3 years were analyzed. Skin (62 %), kidney (58 %), neurological (11 %) and hematologic involvement (76 %) were significantly more common in childhood-onset SLE and disease activity was higher in this subset than in adult- and late-onset disease (SLEDAI-2K 3.4 ± 3.8 vs. 2.2 ± 2.7 vs. 1.6 ± 2.8, respectively; $p = 0.004$). Also, more childhood-onset patients received cyclophosphamide (10 %) and mycophenolate mofetil (34 %). A greater proportion of women (96 %), prevalence of arthritis (89 %) and anti-SSA antibodies (34 %) were noted in the adult-onset group. There was a significant delay in the diagnosis of SLE in older ages. Co-morbidities such as hypertension, diabetes and thyroid disease were significantly more frequent in late-onset SLE, as well as the presence of irreversible damage evaluated by the SLICC/ACR damage index (20 vs. 26 vs. 40 %; $p < 0.001$). Greater organ involvement as well as the frequent need for immunosuppressants supports the concept of childhood-onset being a more severe disease. In contrast, disease onset is more indolent but co-morbidity burden and irreversible damage are greater in late-onset SLE, which may have implications for patients' management.

Keywords Systemic lupus erythematosus · Reuma.pt · Register · Portugal

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Introduction

Systemic lupus erythematosus (SLE) is a multisystem autoimmune disease with a highly variable presentation and course that predominantly affects women of reproductive age [1–4].

However, approximately 15–20 % of patients develop SLE prior to adulthood and about 2–20 % experience disease onset after the age of 50 [5–8]. In a previous analysis of the Portuguese SLE population, 75 % of

patients were diagnosed between 16 and 49 years old. The childhood-onset was uncommon, observed in only 38 patients (7 %) and whereas late-onset was the case for in 92 patients (18 %) [9]. The age at diagnosis has a strong modulating effect on clinical presentation, course of illness, response to treatment and also on prognosis [1, 3, 4], but the findings are not always consistent across studies. Heterogeneous follow-up and disease duration are among the reasons for these discrepancies. Several reports showed that childhood-onset SLE is more severe, with higher rates of major organ involvement, namely more renal, neurologic, and hematologic disorders. Despite more insidious onset of disease and less major organ involvement [1–3, 10], organ damage seems to be more common in late-onset SLE [1, 10]. A cross-sectional analysis of SLE patients from the Portuguese Lupus register Reuma.pt/SLE in whom damage assessment using the SLICC/ACR-Disability Index (SDI) was performed showed SDI $\geq$ 1 in 37 % patients, of whom 24 % had severe damage. Musculoskeletal (24.4 %), neuropsychiatric (24.1 %) and ocular (17.2 %) domains were the most commonly affected [11].

The rheumatic diseases register of the Portuguese Society of Rheumatology (Reuma.pt) launched in September 2012 a longitudinal observational register for SLE patients—the Reuma.pt/SLE. Registers are crucial to understand the course, long-term outcome and burden of the disease and represents also an important source of information on effectiveness and safety of treatments, thus contributing for a better use of medications and ultimately for improvement of rheumatic patients care [12].

After providing signed informed consent, 1510 patients with SLE were retrospectively included in Reuma.pt/SLE between September and December 2012, and prospectively followed afterward. All patients have a baseline assessment where demographics, education, lifestyle habits, ACR and SLICC classification criteria for SLE, disease activity, pregnancy morbidity, and thrombotic events, accumulated damage, co-morbidities and medication were recorded. Follow-up visits were conducted every 3–4 months, according to clinical practice [11, 12].

With this study we aim to characterize the groups of SLE patients with childhood, adult and later onset disease in a multicentre, nation-wide SLE register, describing demographic and clinical characteristics, presence of co-morbidities, accumulated damage, laboratory variables, (including auto-antibodies profile), and treatment use, and assess disease outcomes. Additionally, we aim to compare childhood-onset with randomly selected patients with SLE of later onset, matched for disease duration, to understand the influence of age at disease onset on the outcomes, namely in accumulated damage.

Materials and methods

This study encompasses a cross-sectional analysis that compares three different onset disease groups of SLE patients, with the same disease duration.

Patients

All patients registered until December 31, 2013, in Reuma.pt/SLE fulfilling at least 4 of the 1997 American College of Rheumatology (ACR) revised criteria for SLE were included. Patients with incomplete lupus or with other rheumatic diseases, except secondary Sjögren's syndrome or secondary antiphospholipid syndrome, were excluded. In total 1296 SLE patients were enrolled, of whom, patients with childhood onset defined as diagnosis at the age of 18 or younger were identified ($N = 89$), and compared with randomly selected adult-onset ($\geq$19 and $\leq$49 years) and late-onset ($\geq$50 years) counterparts matched 1:1:1 for disease duration.

Variables

We analyzed the following variables: age, gender, ethnicity, educational level, age at disease onset defined by the first manifestations attributable to SLE, disease duration, cumulative clinical manifestations, disease activity assessed using the Systemic Lupus Erythematosus Disease Activity Index 2000-(SLEDAI 2K) [13] at last visit, damage assessed by the System Lupus International Collaborating Clinics/ACR Damage Index for Systemic Lupus Erythematosus—SDI [14] at last visit and medications (previous and current use). Co-morbidities analyzed included hypertension, diabetes, thyroid diseases, secondary Sjögren's syndrome and antiphospholipid syndrome, according to the accepted definitions.

Missing data were retrieved, whenever possible, by reviewing all available medical records. The time of diagnosis was defined as the time of clinical diagnosis of SLE established by an attending rheumatologist experienced in SLE. Disease duration was defined as the interval between date of diagnosis and date of last visit. Diagnosis delay was defined as the time between first symptom/manifestation attributable to SLE and the date of clinical diagnosis established by the treating physician.

Statistical analysis

A cross-sectional analysis of this cohort was made at the last registered visit. Continuous variables are expressed as mean $\pm$ standard deviation, if they have a normal distribution or median with interquartile range if not normally

distributed. Categorical variables are presented as absolute values and frequencies. Groups were compared using Chi-square tests, Kruskal–Wallis tests, ANOVA and Bonferroni correction for multiple comparisons. Regression analysis was used to assess the association between age at SLE diagnosis and disease characteristics and outcomes. A significance level of 5 % was used in all analyses. All statistical analyses were performed using Stata, version 12.0.

Results

In total, 267 SLE patients with disease duration of 11.9 ± 9.3 years were included in our analysis. Demographic and clinical features are shown in Table 1.

Comparing the three groups, patients with adult-onset SLE have a statistically higher female predominance. No difference in race distribution was found. Patients with disease onset ≤18 years had a higher number of ACR SLE criteria fulfilled. Childhood-onset SLE was positively associated with the presence of malar rash (OR 2.89; 95 % CI 1.17–4.92), renal involvement (OR 4.92; 95 % CI 2.83–8.55), neurologic disorder (OR 3.19; 95 % CI 1.17–8.71) and hematologic disorder (OR 4.15; 95 % CI 1.97–8.46). Also, it is worth mentioning that low complement was more frequent in childhood-onset group (OR 4.05; 95 % CI 1.94–8.43). In contrast, arthritis (OR 3.27; 95 % CI 1.46–7.29) and anti-SSA positivity (OR 2.49; 95 % CI 1.29–4.79) were positively associated with adult-onset SLE. Disease activity assessed by SLEDAI-2K at last visit was significantly higher in the group with childhood-onset onset (Fig. 1). A greater diagnosis delay was observed in late-onset group.

The proportion of patients with accumulated damage measured by SLICC damage index (SLICC ≥ 1) was significantly different between groups, being higher in the older group (OR 3.13; 95 % CI 1.72–5.58) (childhood-onset 20 % vs. adult-onset 26 % vs. late-onset 40 %, $p < 0.005$). Also co-morbid conditions were significantly associated with older age at SLE diagnosis, especially hypertension (OR 3.59; 95 % CI 2.01–6.39), diabetes (OR 4.36; 95 % CI 1.69–11.15) and thyroid disease (OR 2.55; 95 % CI 1.24–5.27) (Table 2).

The most frequently prescribed therapies are described in Table 3. Approximately 67 % of patients received glucocorticoids, without differences between groups. On the

Table 1 Demographic and clinical characteristics of SLE patients included in analysis

Feature	Childhood-onset $N = 89$	Adult-onset $N = 89$	Late-onset $N = 89$	p
Female (%)	77 (87)	85 (96)	78 (88)	**0.039**
Current mean age (years)	25.1 ± 9.1	40.0 ± 13.1	68.3 ± 7.3	**<0.001**
Age at diagnosis (years)	13.4 ± 5.5	29.1 ± 7.5	54.8 ± 5.5	**<0.001**
Diagnosis delay (years)	0.54 ± 5.03	2.01 ± 3.05	3.25 ± 4.06	**<0.001**
Ethnicity, $N = 234$				
Caucasian	78	72	68	0.418
African	3	7	1	
Others	4	0	1	
Number of ACR criteria fulfilled	5.8 ± 1.3	5.3 ± 1.3	5.2 ± 1.1	**0.005**
Malar rash (%)	55 (62)	32 (36)	33 (37)	**<0.001**
Discoid rash (%)	3 (3)	6 (7)	9 (10)	0.221
Photosensitivity (%)	41 (46)	53 (60)	42 (47)	0.101
Oral ulcers (%)	29 (33)	31 (35)	33 (37)	0.839
Arthritis (%)	62 (70)	79 (89)	71 (80)	**0.005**
Serositis (%)	23 (26)	17 (19)	30 (34)	0.115
Renal involvement (%)	52 (58)	28 (31)	14 (16)	**<0.001**
Neurologic disorder (%)	10 (11)	5 (6)	2 (2)	**0.039**
Hematologic disorder (%)	68 (76)	53 (62)	67 (75)	**0.029**
Immunologic disorder (%)	84 (94)	77 (87)	78 (88)	0.508
Positive antinuclear antibodies (%)	86 (97)	88 (99)	88 (99)	0.508
Low complement (%)	74(83)	60 (67)	46 (52)	**<0.001**
Anti-SSA positivity (%)	13 (15)	30 (34)	19 (21)	**0.006**
Anti-SSB positivity (%)	8 (9)	11 (12)	11 (12)	0.927
SLEDAI-2K at last visit	3.4 ± 3.8	2.2 ± 2.7	1.6 ± 2.8	**0.004**

Statistically significant p-values are shown in bold

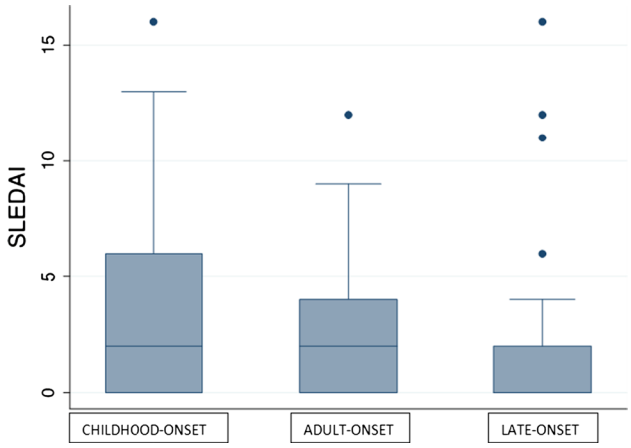

Fig. 1 SLEDAI 2K at last visit

contrary, cyclophosphamide and mycophenolate mofetil were statistically significantly more prescribed in patients with childhood-onset. Exposure to other immunosuppressant drugs, including azathioprine, cyclosporine, methotrexate, and biological therapies were similar among the three groups.

Discussion

This study compares SLE patients from similar ethnic and environmental backgrounds with long-standing disease and different ages at disease onset, matched for disease duration, which contributes to the understanding of the effect of age on disease phenotype and disease outcomes. The sample size is powered to detect significant differences in SLEDAI (94 % power, 95 % CI, $\alpha = 0.05$) and a 20 % difference in the presence of damage (85 % power, 95 % CI, $\alpha = 0.05$) between childhood and late-onset SLE.

We found that age at disease onset influenced clinical and serological findings of SLE, as well as the occurrence of irreversible damage.

The female predominance was more marked in adult-onset, which is in line with published data [3–5]. Of interest, we found a median interval between symptom onset and SLE diagnosis significantly higher in late-onset group possibly due to a more insidious disease onset, milder clinical manifestations and also lower physicians' awareness regarding SLE diagnosis in this age group [6, 7]. Alonso et al. and Tomic-Lucic et al. showed the same tendency [6, 7].

Table 2 Long-term disease outcomes of SLE patients according to age at disease onset

Feature	Childhood-onset $N = 89$	Adult-onset $N = 89$	Late-onset $N = 89$	p
SLICC-DI	0.5 ± 0.9	0.7 ± 1.3	0.9 ± 1.3	0.116
SLICC-DI ≥ 1 (%)	18 (20)	23 (26)	36 (40)	**<0.001**
Hypertension (%)	17 (19)	16 (18)	43 (48)	**<0.001**
Diabetes (%)	3 (3)	5 (6)	10 (11)	**0.008**
Hypercholesterolemia (%)	2 (2)	5 (6)	2 (2)	0.384
Thyroid disease (%)	3 (3)	13 (26)	20 (23)	**0.004**
Antiphospholipid syndrome (%)	10 (11)	11 (12)	6 (7)	0.267
Sjögren's syndrome (%)	2 (2)	5 (6)	10 (11)	0.101

Statistically significant p-values are shown in bold

Table 3 Medication used for SLE

Feature	Childhood-onset $N = 89$	Adult-onset $N = 89$	Late-onset $N = 89$	p
Antimalarial drugs (ever) (%)	68 (76)	72 (84)	63 (71)	0.182
Glucocorticoids (ever) (%)	65 (73)	60 (67)	53 (60)	0.125
Other immunosuppressants (ever)				
Azathioprine (%)	26 (29)	21 (24)	27 (30)	0.999
Methotrexate (%)	10 (11)	13 (15)	14 (16)	0.657
Cyclophosphamide (%)	9 (10)	3 (4)	1 (1)	**0.019**
Cyclosporine (%)	6 (7)	2 (2)	0 (0)	0.332
Mycophenolate mofetil (%)	30 (34)	7 (8)	4 (5)	**<0.001**
Biological therapies (ever) (%)	8 (9)	9 (10)	1 (1)	0.847

Statistically significant p-values are shown in bold

The childhood-onset group fulfilled a higher number of ACR criteria and also presented more frequently malar rash and major organ involvement than older patients [6]. Other cohorts also found nephritis, anemia, thrombocytopenia and neurological disorder to be more common in childhood-onset SLE [1, 4, 15, 16], while serositis and Sjögren's syndrome were more commonly reported in adult-onset patients [4]. Alonso et al. [6] demonstrated a striking decline in the incidence and severity of renal disease in older patients, as well as a lower frequency of seizures and psychosis. In contrast, Feng et al. [3] analyzed a total of 1898 SLE patients and found no differences in major organ involvement among groups defined by age of SLE onset. Nevertheless, a recent meta-analysis of 905 childhood-onset and 59,993 adult-onset patients confirmed that thrombocytopenia, urinary casts, seizures and hemolytic anemia are all more commonly found in childhood-onset [5]. Taken together, these findings reinforce the need for closer monitoring of young SLE patients.

We found arthritis and anti-SSA positivity to be more common in adult-onset patients. According to some reports, sicca syndrome is more common among adult-onset patients [5, 6, 17], but in our cohort most cases of positive anti-SSA antibodies did not translate in sicca symptoms. We did not observe any differences regarding the positivity of other auto-antibodies.

Comparing to adult-onset, childhood-onset has been reported as having a more serious disease course with higher SLE disease activity and more rapid development of damage [3, 18–22]. Some studies revealed that childhood-onset carries a more elevated mortality risk than adult-onset and late-onset, being an independent predictor of mortality [5, 18, 19, 21]. A more recent study by Tucker et al. [16] found adolescent SLE patients had more active disease, higher damage accrual, and a twofold higher mortality rate that adult-onset SLE patients. In our cohort, childhood-onset was also related to higher disease activity measured by SLEDAI-2K, although the mean disease activity was lower than reported in other cohorts [21]. The frequently reported association of childhood-onset SLE with inherited complement and immunoglobulin deficiency states [23] might impact the disease severity in this age group.

Additionally, childhood-onset patients were more likely to have received immunosuppressant therapy, suggesting more severe overall disease. Childhood-onset subjects received more mycophenolate mofetil and cyclophosphamide, two drugs commonly used to treat severe manifestations, including lupus nephritis and central nervous system involvement.

Co-morbidities such as hypertension and diabetes were more prevalent in late-onset patients, as expected. These findings advise regular screening and adequate control of co-morbidities in order to avoid irreversible damage. Thyroid pathology is frequent among lupus patients [24] and to the best of our knowledge, this is the first study demonstrating its increase in late-onset SLE patients. The awareness of this high prevalence is important, since some symptoms of thyroid disorders are non-specific and may mimic SLE manifestations.

Our results corroborate recent studies demonstrating that organ damage is greater in late-onset group [3, 7]. Furthermore, some authors describe a trend toward high mortality in late-onset, despite the fact that an older population has a remaining life expectancy lower than that of young people, regardless of SLE. Given these findings it is questionable to classify late-onset as a benign disease. Cumulative damage certainly reflects not only the effect of the disease per se, but also the effect of aging and the increased likelihood of co-morbid conditions, such as cardiovascular disease, infections and drug-induced complications. Globally, the mean SDI of our cohort is relatively low given the long disease duration. This fact can be explained by several reasons. Primarily, Reuma.pt/SLE includes patients not only from tertiary referral centers, but also from community rheumatology practices where milder SLE cases are followed. Also, this is not an inception cohort and the most serious and potentially fatal cases may be under-represented. Another possible explanation for the low damage could be due to timely used therapy in more recent years, thereby preventing damage observed in historical cohorts.

This study has some limitations. First of all, Reuma.pt/SLE is not an inception cohort and data was retrospectively collected until September 2012. It is conceivable that patients with more severe disease that could have result in premature death or severe disability and those lost to follow-up for other reasons are not represented, but this is true for the 3 age groups. Secondly, we included 267 SLE patients, which might not be enough for some analyses. Finally, SLICC-DI measurement does not allow the distinction between damage as consequence of disease itself from damage resulting from the aging process and our study did not include other outcome measures such as mortality. We will address this in future research.

In summary, while childhood-onset SLE is a more severe disease, late-onset SLE has a more indolent course but patients have more co-morbidities and acquire more irreversible damage. Physicians should be aware of these differences, which may have impact on SLE diagnosis and disease management.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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