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Comparison of Clinical and Laboratory Findings in Patients with Systemic Lupus Erythematosus with Regard to Age at Onset

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ABSTRACT

Objective: Systemic lupus erythematosus (SLE) rarely has a late onset. Late-onset SLE (LSLE) has a milder course and less organ involvement. The purpose of the present study was to compare the clinical and laboratory (lab) findings of SLE regarding age at onset.

Materials and Methods: Seventy-two patients with SLE were included in the study. The age at onset was considered adult-onset SLE (ASLE) if it was <50 years and LSLE if it was ≥50 years. Lab parameters and clinical findings were compared accordingly.

Results: Overall, 41 (56.9%) patients had ASLE, and 31 (43.05%) patients had LSLE based on the age at onset. The ratio of female-to-male patients was higher in ASLE, and no significant difference was found with regard to gender distribution (12.6:1 and 5.2:1 for ASLE and LSLE, respectively; p=0.239). While malar rash and fever were more common in ASLE, no difference was found regarding the other clinical findings. Only IgG anti-cardiolipin was more common in LSE between the lab parameters.

Conclusion: Although it is known that LSLE has a milder course and less organ involvement, there are differences in clinical and lab findings and organ involvement in various studies. The results of our study showed no significant difference in organ involvement between ASLE and LSLE.

Keywords: Age onset, clinical manifestations, laboratory findings, systemic lupus erythematosus

Introduction

Systemic lupus erythematosus (SLE) is an autoimmune disease with unclear etiopathogenesis, which can involve many organs and systems [1]. Although SLE is most commonly seen in women of child-bearing age, it can present at any age [2]. The age at onset of the disease as well as ethnicity affects the severity and clinical findings of the disease. Studies revealed that juvenile-onset SLE (JSLE, <18 years) has a more aggressive course than adult-onset disease and involves more organs [3, 4], whereas late-onset SLE (LSLE, ≥50 years) starts more stealthily, has less organ involvement, and follows a more benign course [5, 6]. However, the prognosis is worse in LSLE due to aging and exposure to vascular risk factors for a longer period, thus causing more comorbid diseases and more organ damage [7–9].

As SLE is more common in women of reproductive age, the time from onset of symptoms to diagnosis in pediatric, male patients with LSLE is longer than that in patients with adult-onset SLE (ASLE) [10, 11].

The purpose of the present study was to compare the clinical and laboratory (lab) parameters in patients diagnosed with SLE with regard to age at disease onset.

Materials and Methods

A total of 72 patients who were followed up with a diagnosis of SLE between January 2013 and July 2017 and who have data from their period of diagnosis were included in the study. Approval for the present study was obtained from the ethics committee of Adnan Menderes University for non-invasive clinical studies (no. 2017/1204). No informed consent was available since this was a retrospective study.

All patients met the American College of Rheumatology revised criteria for the classification of SLE [12, 13].

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Table 1. Demographics and lab parameters based on age at disease onset.

	Total (n=72)	SLE <50 years (n=41)	SLE ≥50 years (n=31)	p
Age at diagnosis, years	43.2 (±19.25)	29.12±10.6	61.8±9.8	0.000
Female gender, n (%)	64 (88.9)	38 (92.7)	26 (83.9)	0.239
Family history of SLE, n (%)	2 (2.8)	2 (4.9)	0 (0)	0.212
Leukopenia, n (%)	14 (19.4)	10 (24.4)	4 (12.9)	0.223
Anemia, n (%)	28 (38.9)	14 (34.1)	14 (45.2)	0.342
Thrombocytopenia, n (%)	13 (18.1)	8 (19.5)	5 (16.1)	0.712
Low C3, n (%)	34 (47.2)	22 (53.7)	12 (38.7)	0.208
Low C4, n (%)	43 (59.7)	24 (58.5)	19 (61.3)	0.814
Coombs positivity, n (%)	26 (36.1)	13 (35.1)	13 (52.0)	0.187
ANA positivity, n (%)	60 (92.3)	32 (88.9)	28 (96.6)	0.249
dsDNA, n (%)	32 (44.4)	15 (50)	17 (58.6)	0.506
SS-A, n (%)	13 (18.1)	8 (26.7)	5 (17.9)	0.421
Ro-52, n (%)	12 (16.7)	5 (16.1)	7 (25)	0.398
SS-B, n (%)	4 (5.6)	1 (3.3)	3 (10.7)	0.268
RNP/Sm, n (%)	15 (20.8)	10 (33.3)	5 (17.9)	0.179
Nucleosomes, n (%)	15 (20.8)	7 (23.3)	8 (28.6)	0.649
Histones, n (%)	7 (9.7)	4 (12.9)	3 (10.7)	0.795
Ribosomal-P, n (%)	2 (2.8)	1 (3.1)	1 (3.7)	0.903
PM-Scl, n (%)	1 (1.4)	0 (0)	1 (3.6)	0.289
Centromere, n (%)	2 (2.8)	0 (0)	2 (7.4)	0.117
PCNA, n (%)	1 (1.4)	0 (0)	1 (3.6)	0.289
aCL-IgM, n (%)	4 (5.6)	1 (2.43)	3 (9.67)	0.364
aCL-IgG, n (%)	16 (22.2)	4 (9.8)	12 (38.7)	0.014

C: complement; ANA: antinuclear antibody; RNP/Sm: ribonucleoprotein/Smith; SS-A: Sjögren's syndrome-A; SS-B: Sjögren's syndrome-B; PM-Scl: polymyositis–systemic sclerosis; dsDNA: double-stranded DNA; ribosomal-P: ribosomal protein; PCNA: proliferating cell nuclear antigen; aCL: anti-cardiolipin antibody.

Patients were divided into two groups based on their age at disease diagnosis. Age at onset was considered ASLE if it was <50 years and LSLE if it was ≥50 years, as this is the most commonly used cut-off age in most protocols [14–17].

Patients with drug-related lupus, only diagnosed with cutaneous lupus, and with another concomitant systemic rheumatic disease were excluded in the study.

The patients' age at diagnosis, family history, clinical and lab findings at the time of diagnosis, disease activity at the time of diagnosis, treatments, and fatality, if any, were recorded. The existence of SLE in first-degree family members of the patients was considered family history.

Clinical signs included photosensitivity, malar rash, discoid rash, oral ulcers, arthritis, serositis, renal involvement, central nervous system involvement, fever, Raynaud's phenomenon, and interstitial lung disease. SLE disease activity index (SLEDAI) was used to assess disease activity [18].

Antinuclear antibody (ANA) tests were performed by indirect fluorescence antibody method (performed with Hep2 cells with a cut-off of >1/100). Autoantibodies, such as ribonucleoprotein/Smith (RNP/Sm), Sjögren's syndrome-A (SS-A), Ro-52, Sjögren's syndrome-B, polymyositis–systemic sclerosis, centromere B, double-stranded DNA (dsDNA), nucleosomes, histones, ribosomal protein, and proliferating cell nuclear antigen, were assessed by immunoblot technique. IgG and IgM anticardiolipin (aCL) antibody tests were performed with enzyme-linked immunosorbent assay (positive assay; aCL-IgM >18 MPLU/mL and aCL-IgG >18 GPLU/mL).

Treatments received by the patients throughout their diseases, such as antimalarial, cyclophosphamide, azathioprine, methotrexate, mycophenolate mofetil, rituximab, plasmapheresis, intravenous immunoglobulin, and corticosteroids, were recorded.

Concomitant diseases, such as chronic obstructive pulmonary disease (COPD), asthma, antiphospholipid syndrome (APS), thyroid disease, diabetes mellitus (DM), hypertension (HT), and coronary artery disease (CAD), were recorded.

Statistical Analysis
Statistical analysis was performed using the SPSS software (IBM, SPSS Corp.; Armonk, NY, USA) version 18.0 for Windows. Values were expressed as mean±standard deviation for continuous variables and percentages for categorical variables. For statistical analysis, Mann–Whitney U and chi-square tests were used for dependent groups. Type 1 error level was considered as 0.05.

Results
The average age at diagnosis of 72 patients with SLE was 43.2 (±19.25) years, and the ratio of female-to-male (F/M) patients was 8:1. A review of the patients' first-degree family members showed that 2 (2.8%) patients had a family history. There were 14 (19.4%) patients with leukopenia, 28 (38.9%) with anemia, 13 (18.1%) with thrombocytopenia, and 34 (47.2%) and 43 (59.7%) with hypocomplementemia (C) C3 and C4, respectively. There

Table 2. Clinical features, treatment, and mortality based on age at onset of the disease.

	Total (n=72)	SLE <50 years (n=41)	SLE ≥50 years (n=31)	p
Photosensitivity, n (%)	4 (5.6)	1 (2.4)	3 (9.7)	0.184
Malar rash, n (%)	16 (22.2)	14 (34.1)	2 (6.5)	0.005
Discoid rash, n (%)	3 (4.2)	1 (2.4)	2 (6.5)	0.399
Oral ulcers, n (%)	3 (4.2)	2 (4.9)	1 (3.2)	0.728
Arthritis, n (%)	50 (69.4)	31 (75.6)	19 (61.3)	0.192
Serositis, n (%)	6 (8.3)	3 (7.3)	3 (9.7)	0.720
Renal involvement, n (%)	32 (44.4)	22 (53.7)	10 (32.3)	0.070
Hematologic involvement, n (%)	27 (37.5)	17 (41.5)	10 (32.3)	0.424
Neurologic involvement, n (%)	2 (2.8)	1 (2.4)	1 (3.2)	0.841
Fever, n (%)	5 (6.9)	5 (12.2)	0 (0)	0.044
Raynaud's phenomenon, n (%)	6 (8.3)	4 (9.8)	2 (6.5)	0.615
ILD, n (%)	5 (6.9)	1 (2.4)	4 (12.9)	0.084
SLEDAI	10.44±4.28	11.09±4.42	9.58±3.98	0.207
Corticosteroid, n (%)	71 (98.6)	41 (100)	30 (96.8)	0.247
Cyclophosphamide, n (%)	17 (23.6)	10 (24.4)	7 (22.6)	0.858
Antimalarial, n (%)	70 (97.2)	41 (100)	29 (93.5)	0.099
Azathioprine, n (%)	29 (40.3)	22 (53.7)	7 (22.6)	0.008
Mycophenolate mofetil, n (%)	11 (15.3)	10 (24.4)	1 (3.2)	0.013
Rituximab, n (%)	6 (8.3)	5 (12.2)	1 (3.2)	0.173
Methotrexate, n (%)	4 (5.6)	4 (9.8)	0 (0)	0.074
Plasmapheresis, n (%)	1 (1.4)	0 (0)	1 (3.2)	0.247
Intravenous immunoglobulin, n (%)	2 (2.8)	2 (4.9)	0 (0)	0.212
Death, n (%)	1 (1.4)	0 (0)	1 (3.2)	0.247

ILD: interstitial lung disease; SLEDAI: SLE disease activity index.

Table 3. Concomitant comorbid diseases.

	Total (n=72)	SLE <50 years (n=41)	SLE ≥50 years (n=31)	p
COPD, n (%)	3 (4.2)	1 (2.4)	2 (6.5)	0.399
Asthma, n (%)	5 (6.9)	3 (7.3)	2 (6.5)	0.886
APS, n (%)	2 (2.8)	0 (0)	2 (6.5)	0.099
Thyroid disease, n (%)	9 (12.5)	2 (4.9)	7 (22.6)	0.025
DM, n (%)	4 (5.6)	1 (2.4)	3 (9.7)	0.184
HT, n (%)	18 (25)	6 (14.6)	12 (38.7)	0.019
CAD, n (%)	4 (5.6)	0 (0)	4 (12.9)	0.018

COPD: chronic obstructive pulmonary disease; APS: antiphospholipid syndrome; DM: diabetes mellitus; HT: hypertension; CAD: coronary artery disease.

were 26 (36.1%) patients with Coombs positivity. In total, 92.3% of the patients were ANA positive, and the most common autoantibodies were dsDNA (44.4%), RNP/Sm (20.8%), nucleosome (20.8%), SS-A (18.1%), and Ro-52 (16.7%). There were 5.6% of the patients who were IgM-aCL positive and 22.2% who were IgG-aCL positive (Table 1).

The most common clinical findings were arthritis (69.4%), renal involvement (44.4%), and hematologic involvement (37.5%) (Table 2).

Overall, 41 (56.9%) patients had ASLE, and 31 (43.05%) patients had LSLE based on the age at disease onset. The ratio of F/M patients was higher in ASLE, and no significant difference was found with regard to gender distribution (12.6:1 and 5.2:1 for ASLE and LSLE, respectively; p=0.239). No significant difference was found between the two groups with regard to family history. Only IgG-aCL was higher in LSLE between the lab findings (p=0.014) (Table 1).

While malar rash and fever were more common in ASLE (p=0.005 and p=0.044, respec-

tively), no significant difference was found with regard to the other clinical features (Table 2).

There was no difference with regard to drugs other than azathioprine and mycophenolate used as treatment agents (p=0.008 and p=0.013, respectively) (Table 2).

Of the concomitant comorbid diseases, while thyroid disease, HT, and CAD were more common in LSLE (p=0.025, 0.019, and 0.018, respectively), no difference was found with regard

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to the other comorbid diseases, such as COPD, asthma, APS, and DM (Table 3). One patient with LSLE died due to infection.

Discussion

Age at onset older than 50 years is rare in SLE, and this is called LSLE. In our study, the percentage of late-onset lupus was found to be 43.05%, which is higher than in the literature (12.4% in Korean patients, 4.76% in British patients, 15.05% in Brazilian patients, and 6.9% in Latin American patients) [17, 19–21]. The fact that this disease is more common in reproductive age can delay diagnosis in older patients. In addition, ethnic differences can affect the prevalence of LSLE.

The ratio of F/M patients was 8:1 and was 12.6:1 in ASLE and 5.2:1 in LSLE. These findings are consistent with the literature, and the decrease in this ratio among genders as patients become older supports the finding that estrogen plays a role in pathogenesis [22, 23].

Age at disease onset affects its clinical signs and the course of the disease. The most commonly accepted opinion is that LSLE has a stealthier and milder route. Compared with ASLE and JSLE, less disease activity, less organ involvement, and less renal involvement are seen in LSLE [7, 24, 25].

In our study, the most common clinical findings were similar in both groups and were arthritis, renal involvement, and hematological involvement in order of frequency. While malar rash and fever were more common in ASLE, no difference was found regarding the other clinical findings. Although arthritis, renal involvement, and hematological involvement were more common in ASLE, it was not significant. Furthermore, SLEDAI was not different in the two groups. Similar to our study, Feng et al. [6] investigated 1898 patients with SLE and did not find any difference regarding disease activity and significant organ involvement.

In studies conducted for mucocutaneous findings, different results have been obtained for different ethnicities. Mucocutaneous findings, such as malar rash, photosensitivity, oral ulcers, and Raynaud's phenomenon, are more common in ASLE in Latin America, only malar rash is more common in JSLE and ASLE than in LSLE in Brazil, and only oral ulcers are more common in JSLE and ASLE in Korea [17, 19, 21]. It has been shown that oral ulcers are more common in JSLE, and alopecia becomes less with age in UK [20]. In our study, we found that malar rash, which is a mucocutaneous finding, is more common in ASLE.

It is known that although the disease has a more benign course in LSLE, organ damage and mortality are higher. In the study by Catoggio et al. [21], the mortality rate is found higher in LSLE, but it is not stated whether the deaths are associated with infection or SLE. In the study by Feng et al., it was shown that mortality rate is higher in LSLE (>45 years), and half of these deaths are due to infections, and that the causes due to SLE are at a similar percentage [6]. In our study, one patient with LSLE died, and the cause of her death was infection. Although we have observed that all comorbid diseases increase with age, the fact that only one patient died can be associated with the short duration of the study.

No significant difference was found between the lab parameters except IgG-aCL in our study. Although some of the studies suggested that ds-DNA is less frequent in LSLE, and this is because renal involvement is less frequent, some other studies showed that there is no difference between the age groups [6, 19, 21, 26]. The fact that we have not seen significant differences in organ involvement or disease activity can be suggestive that no distinction is seen with regard to autoantibodies. In addition, no difference was found regarding anemia, thrombocytopenia, leukopenia, and hypocomplementemia in line with disease activity and organ involvement. In SLE, 30%–40% of patients are positive for antiphospholipid antibodies, and aCL varies between 17% and 40%. The prevalence of clinical manifestations in patients with lupus is approximately 20% [27–30]. In our study, IgM-aCL positive was 5.6%, and IgG-aCL positive was 22.2% similar with the literature. IgG-aCL positive is more common in LSLE. However, only 2 (2.8%) patients had APS, and our results were lower than the literature.

The fact that there is no significant difference between the two groups when the clinical findings are assessed, and the disease activity is similar, can be suggestive that there is no difference between the corticosteroids, cyclophosphamide, and antimalarials used for treatment. In our study, only azathioprine and mycophenolate mofetil, two of the other immunosuppressive agents, were more commonly used in ASLE.

The fact that the present study was designed as a retrospective and single-center study, and medical records up to the year 2013 only could be obtained, as well as the small number of subjects, were limitations of the study.

Consequently, clinical and lab findings and organ involvement of LSLE in various studies are different. In our study, we have shown that there

was no difference except for malar rash and fever with regard to age at onset in our region.

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