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Original Article

Delay in the Diagnosis of SLE: The Importance of Arthritis/Arthralgia as the Initial Symptom

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Despite the current diagnostic and serologic testing for SLE, the interval between the onset of symptoms and the diagnosis is still long. In this study, we aimed to show the interval between the initial symptoms and the diagnosis of SLE and to investigate the presence of any relationship between the interval and the initial symptoms. One hundred and thirty-six patients were diagnosed with SLE using the 1982 ARA criteria. The mean age of the patients at diagnosis was 29.9 ± 10.5 years. The mean interval between the onset of symptoms and the diagnosis of SLE was 21.82 ± 30.32 months. The subjects were evaluated twice, at intervals of ≤3 and ≤12 months after the onset of symptoms. Although arthritis and/or arthralgia were the most common initial symptoms (60.3%), only 26.8% of the patients with these symptoms were diagnosed earlier than 3 months after the onset. If the first initial symptoms were butterfly rash or pericarditis, pleuritis, spontaneous abortion or cognitive dysfunction, they led to early diagnosis. In conclusion, since arthritis and/or arthralgia are the most common initial symptoms of the disease, every young woman with these symptoms should be carefully evaluated for SLE.

Key words: SLE, arthritis, butterfly rash, delay in SLE diagnosis

Systemic lupus erythematosus (SLE) is a multisystem disease which primarily affects young females and is caused by tissue damage resulting from antibody and complement-fixing immune complex deposition. There is a wide spectrum of clinical presentations. The most common initial symptoms of SLE show cutaneous, musculoskeletal, renal, and hematological involvement. There is no classical pattern, and the diagnosis should be based on an overall view of the clinical signs and laboratory tests [1]. In spite of increased physician awareness and newer diagnostic and serologic testing, the interval between the onset of symptoms and the diagnosis of SLE is still very long [2]. This delay may be due to the characteristics of the first symptom(s) and the sex and age of the patients at the onset of the symptoms.

The aim of this study, a follow-up study in 136 adults with SLE in one center, is to investigate the initial symptoms, the interval between the onset of symptoms and the diagnosis of SLE, the causes of the delay in diagnosis, and the prevalence of SLE-related symptoms.

Materials and Methods

In this follow up study, we evaluated 136 patients with SLE who were diagnosed at Cukurova University Hospital, in the departments of Rheumatology and Nephrology, between April 1991 and September 2002. All of the patients fulfilled the revised criteria for SLE

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established by the American Rheumatism Association [3]. All of the patients were Caucasians living in southern Turkey. The detailed medical histories of the patients were obtained, and initial symptoms were determined chronologically from the onset. The study group comprised 127 women and 9 men. SLE-related symptoms and laboratory tests including complete blood count, erythrocyte sedimentation rate, urinary examination, AST, ALT, total protein, alkaline phosphatase, BUN, creatinine (Cr), creatinine clearance (C_{Cr}), Coomb's test, ANA, anti-dsDNA, and anti-Sm were evaluated. Posteroanterior chest X-Ray, electrocardiogram and echocardiogram were investigated. The time intervals between the initial symptom of the disease and the establishment of a diagnosis were recorded. The word "interval" was accepted to refer to a delay in diagnosis. We also evaluated the association among interval time, characterized as ≤ 3 months or ≤ 12 months, and the initial symptom, and the sex and age of the patient.

Statistical analysis. We tested differences between groups defined by the time delay in their diagnoses using Student's t or the Mann-Whitney U and Kruskal-Wallis tests, when data were nonparametric. $P \leq 0.05$ was considered to be significant.

Results

There were 127 women (93.4%), and 9 men (6.6%), aged 14–60 years. The female-to-male ratio was 14.1:1. The mean age at diagnosis was 29.9 ± 10.5 years (29.8 for women and 27.8 for men). The most common initial symptoms were arthritis and/or arthralgia in 82 (60.3%) patients, followed by butterfly rash in 16 (11.8%), renal involvement in 12 (8.6%), fever in 5 (3.7%), thrombocytopenia in 5 (3.7%), anemia in 4 (2.9%), fatigue, malaise, and weakness in 3 (2.2%), photosensitivity reaction in 3 (2.2%), spontaneous abortion in 2 (1.5%), and cognitive dysfunction, pericarditis, and pleuritis each in 1 (0.8%) (Table 1). The mean interval between the onset of the symptom and the diagnosis of SLE was 21.82 ± 30.32 months. Those patients who had interval times ≤ 3 months (n = 41) and ≤ 12 months (n = 92) are presented in Table 2 along with their initial symptoms. We compared the interval times between patients who had arthritis and/or arthralgia, butterfly rash or renal involvement as their initial symptom and those who did not. We found that SLE was diagnosed earlier in the patients with butterfly rash than in those without butterfly rash [the mean interval time 6.56 ± 8.62 months *vs.* 23.85 ± 31.60 months, respectively, ($P = 0.01$)]. The difference in interval times between patients with arthritis and/or arthralgia and those with renal involvement as their initial symptom was not significant [23.80 ± 32.66 months *vs.* 17.92 ± 25.86 months, ($P > 0.05$), and 22.35 ± 31.27 months *vs.* 15.10 ± 12.43 months, ($P > 0.05$), respectively]. The difference in mean interval time between women and men was not significant [21.85 ± 30.67 months *vs.* 21.33 ± 26.47 months, ($P > 0.05$)].

The subjects were divided into 3 groups according to age at onset of the disease, as follows: Group I: ≤ 20 years (28 patients); Group II: 21–49 years (104 patients); and Group III: ≥ 50 years (4 patients). Interval times for each group were 12.64 ± 2.23 months, 31.36 ± 3.14 months, and 54.88 ± 27.44 months, respec-

Table 1 Initial symptoms at the onset of SLE

Manifestations	n = 136	(%)
Arthritis/arthralgia	82	60.3
Butterfly rash	16	11.8
Renal involvement	12	8.6
Fever	5	3.7
Thrombocytopenia	5	3.7
Anemia	4	2.9
Fatigue, malaise, weakness	3	2.2
Photosensitivity reaction	3	2.2
Spontaneous abortion	2	1.5
Cognitive dysfunction	2	1.5
Pericarditis	1	0.8
Pleuritis	1	0.8

Table 2 Initial symptoms in patients who were diagnosed in ≤ 3 and ≤ 12 months

Manifestations	≤ 3 month[s] n = 41	≤ 12 month[s] n = 92
Arthritis/arthralgia	22/82	54/82
Butterfly rash	8/16	14/16
Renal involvement	2/12	10/12
Fever	0/5	2/5
Thrombocytopenia	3/5	5/5
Anemia	0/4	2/4
Fatigue, malaise, weakness	0/3	0/3
Photosensitivity reaction	0/3	0/3
Spontaneous abortion	1/2	2/2
Cognitive dysfunction	1/2	2/2
Pericarditis	1/1	1/1
Pleuritis	1/1	1/1

tively. There were significant differences between Group I and Group III and between Group II and Group III ($P = 0.01$ for all). There was not any significant difference between Group I and Group II ($P > 0.05$). Data are shown in Table 3.

Discussion

Systemic lupus erythematosus is a systemic disease, with the onset of clinical symptoms usually occurring in the patient's 20s to 30s. Also in our study, the mean age at the diagnosis of SLE was 29.9 ± 10.5 years. In the present study, the most common initial symptoms of SLE were arthritis and/or arthralgia, butterfly rash and renal involvement (60.3%, 11.8%, 8.6% respectively). In similar follow-up studies on SLE, arthritis and/or arthralgia and cutaneous manifestations at the onset of SLE were reported to occur in approximately 80% of patients (60% and 20%, respectively) [4–6]. In another study, it was revealed that skin and mucous membrane involvement (52%), fever and malaise (48%), and arthritis and arthralgia (44%) were the major initial clinical manifestations of SLE [7]. Our results were also found to be consistent with the above and several other studies with respect to the frequency of arthritis and/or arthralgia as chief complaints at the onset of SLE [8, 9].

The mean interval between the onset of symptoms and the diagnosis of SLE was 21.8 ± 30.3 months in our patients. Wallace *et al.* [10] revealed that the interval between the initial symptoms and diagnosis of SLE patients who were diagnosed between 1950 and 1980 was 4.1 years. Later, the same study group investigated patients with SLE between the years 1980 and 1989 and reported that interval to be 2.1 years [2]. In the Eurolupus cohort study of 1000 patients in 1993, a mean 2-year period between the onset of symptoms and diagnosis was documented [11]. Therefore, our findings are similar to the studies mentioned above. In our study, 30.1% of the patients with SLE were diagnosed earlier than 3 months after the onset of symptoms (Table 2).

Which factors influence the delay in the SLE diagnosis? Arthritis and/or arthralgia are the most common initial symptoms in SLE patients when diagnosed ≤ 3 months and ≤ 12 months after the onset of symptoms (22 of 41, 54/92, seen in Table 3). However, in patients with arthritis and/or arthralgia, diagnosis of SLE was not earlier than in patients without these symptoms. But, diagnosis in patients with butterfly rash occurs significantly earlier than in patients without this symptom.

Although arthritis and/or arthralgia are the most common initial symptoms in several other studies in addition to the present study, only 26.8% of the patients with these symptoms are diagnosed earlier than 3 months after the onset of the symptoms (22/82). The cause of

Table 3 Delay in diagnosis: The effects of initial symptom, sex and the patient's age at the onset of diagnosis

Initial symptom	Present or not	N	Delay in diagnosis	Comparison	*P*
Arthritis/arthralgia[a]	Yes	82	23.80 ± 32.66	a *vs.* b	> 0.05
Arthritis/arthralgia[b]	No	54	17.92 ± 25.86		
Butterfly rash[c]	Yes	16	6.56 ± 8.62	c *vs.* d	0.01
Butterfly rash[d]	No	120	23.85 ± 31.60		
Renal involvement[e]	Yes	10	15.10 ± 12.43	e *vs.* f	> 0.05
Renal involvement[f]	No	126	22.35 ± 31.27		
Sex					
Female[g]		127	21.85 ± 30.67	g *vs.* h	> 0.05
Male[h]		9	21.33 ± 26.47		
Age at diagnosis					
≤ 20 years[i]		28	12.64 ± 2.23	i *vs.* j	> 0.05
21–49 years[j]		104	31.36 ± 3.14	j *vs.* k	0.019
≥ 50 years[k]		4	54.88 ± 27.44	i *vs.* k	0.002

this may be that joint involvement is relatively mild and deformity is rare in SLE. Therefore, patients presenting with symptoms of arthritis and/or arthralgia should be evaluated for SLE carefully, so that SLE can be diagnosed earlier, and morbidity and mortality can be decreased. On the other hand, the patients with initial symptoms of pleuritis, pericarditis, cognitive dysfunction, spontaneous abortion, and butterfly rash are diagnosed earlier because life-threatening organ involvement and its symptoms make patients seek urgent medical help, and butterfly rash, a relatively well-known specific finding for SLE, is easily noticed by patients and physicians.

Hochberg *et al*. [12] found that the mean age of onset in men was 40.4 years *vs*. 31.8 years in women (for our patients, 29.8 in women *vs*. 27.8 in men). The disease is difficult to diagnose in older patients (over the age of 50). Also, a comparison of the mean delaying time between women and men does not show a significant difference. A shortcoming of our study is that the number of males (9 patients) and patients over 50 years old (4 patients) was not a large enough basis for a meaningful comparison. However, our findings are also supported by the other studies showing that SLE is often insidious in patients over the age of 50 years [1, 13]. Catoggio *et al*. [13] reported that the duration between symptom onset and diagnosis extended over 48 months in late-onset SLE.

In our study, arthritis and/or arthralgia (86%), butterfly rash (61%) and anemia (55%) were the most common symptoms. These findings are similar to the findings of a number of other studies [2, 3, 5, 14–16]. Other symptoms that have been found include photosensitivity (48%), fever (43%), mouth ulcer (43%), headache (36%), fatigue, malaise, weakness (35%), and alopecia (35%). The renal involvement in the present study was 28%, which is lower than that found in other studies (36% to 47%) [16, 17].

In conclusion, butterfly rash or life-threatening organ involvement leads to early diagnosis of SLE. Arthritis and/or arthralgia are the most common initial symptoms, but they are usually associated with a delay in diagnosis, so every young woman who presents with arthritis and/or arthralgia should be evaluated for SLE.

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