International Scholars Journals

African Journal of Internal Medicine ISSN 2326-7283 Vol. 4 (1), pp. 348-354, January, 2016. Available online at www.internationalscholarsjournals.org © International Scholars Journals

Full Length Research Paper

Systemic lupus erythematosus in children: A study about 37 Tunisian cases

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Accepted 13 May, 2016

The objective of this study was to determine the clinical and serological characteristics of pediatric systemic lupus erythematosus (SLE). This retrospective study included 37 patients with SLE. All patients fulfilled the ACR revised criteria for SLE and diagnosed between 1994 and 2009. Anti-nuclear antibodies were detected by indirect immunofluorescence (IIF) on liver rat sections. Anti-dsDNA, anti-Sm, anti-nucleosome, anti-SSA, anti-SSB and anti-RNP antibodies were detected by ELISA. Anti-dsDNA antibodies were detected also by IIF on *Chrithidia luciliae*. The most common signs were anemia (86.5%), proteinuria (73%) and malar rash (67.6%). The frequency of arthritis and photosensitivity were 45.9% and 43.2% respectively. Leucopenia, thrombocytopenia and oral ulcer were present in 37.8%, 32.4% and 18.9% of cases respectively. The frequency of discoid rash was 13.5%. Anti-dsDNA antibodies were detected in 81.1%, anti-Sm and anti-RNP in 56.8%, anti-SSA in 43.2% and anti-SSB in 35.1%. The highest frequency of childhood SLE is situated at the age of puberty. Renal disease is very frequent in paediatric SLE.

Key words. Systemic lupus erythematosus, renal disease, children, Tunisia.

INTRODUCTION

Systemic lupus erythematosus (SLE) is an autoimmune condition characterized by multiorgan inflammation and autoantibodies production. The course of this disease is characterized by periods of flare and remission, and inflammation can result in irreversible tissue damage, as well as premature death [1]. The etiology remains poorly understood; however, genetic and environmental factors are involved in the pathogenesis [2]. Ten to twenty percent of cases are diagnosed in the first 2 decades of life with a peak incidence at 10-14 years with female predominance, the disease is rare in children below 5 years old [3-5]. It has been suggested that children with SLE had different signs and symptoms at onset and a more severe and aggressive disease course than adult patients [6-8]. Many investigators have described the features of childhood SLE among different ethnic groups [5-21]. The aim of our retrospective study was to determine the clinical and serological characteristics of childhood SLE in the center of Tunisia.

PATIENTS AND METHODS

Study Population

The study cohort consisted of 37 children with SLE. All patients fulfilled the American College of Rheumatology revised criteria for SLE [22]. They were diagnosed at

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pediatric department of four hospitals in the center of Tunisia between 1994 and 2009. All patients were reviewed retrospectively for demographic characteristics, clinical and laboratory variables. The study was approved by local Ethics Committee and all patients and/or their parents gave their informed consent.

METHODS

Anti-nuclear antibodies (ANA) were detected by indirect immunofluorescence (IIF) on liver rat sections as described previously [24]. The anti-double stranded DNA (dsDNA), anti-Sm, anti-SSA, anti-SSB and anti-RNP antibodies were detected by ELISA (ORGENTEC®, Mainz, Germany). Anti-dsDNA antibodies were detected also by IIF in *Chrithidia luciliae* (ORGENTEC®).

RESULTS

Out of 342 SLE patients diagnosed between 1994 and 2009, 37 were children and 18 were elderly. In this group of children, there were 28 girls and 9 boys (F/M ratio: 3.1). The mean age at diagnosis was 11.5 years (range, 9 months to 15 years) (Table 1). These patients were divided in two groups; 17 who are aged between 9 months and 12 years (45.9%), and 20 who are older than 12 years (54.1%). Figure 1 shows the distribution of SLE patients according to age and sex.

Table 2 summarizes the frequencies of the clinical features of SLE. The most common sign was anemia (86.5%). The frequencies of malar rash, photosensitivity, oral ulcer and discoid rash were 67.6%, 43.2%, 18.9% and 13.5% respectively. Arthritis, neuropsychiatric, pleuritis and pericarditis were found in 45.9%, 13.5%, 10.8%, and 8.1% of cases respectively. ANA were detected in all patients (100%). The anti-dsDNA antibodies were detected in 81.1%, anti-Sm and anti-RNP in 56.8%, anti-SSA in 43.2% and anti-SSB in 35.1% (Table 3).

Twenty-seven SLE patients out of 37 had proteinuria (73%) (Table 2). Thirteen patients out of 27 with proteinuria underwent renal biopsy. According to WHO classification [23]: 7 patients out of 13 (53.8%) had class IV lupus nephritis, 4 patients had class III and 2 patients had class V nephritis (Table 2). All these patients had anti-dsDNA (100%), 69.2% had anti-Sm, 38.5% had anti-SSA, 46.2% had anti-SSB and 61.5% had anti-RNP antibodies (Table 4).

Corticoids were prescribed in 78.4% of patients. In fact, cortancyl was prescribed in 73% of cases, solumedrol in 24.3% and nivaquine in 18.9%. Eight patients (21.6%) were handled with immunosuppressive therapy which was cyclophosphamide.

Eight out of 37 children (21.6%) were died. Six patients out of these were treated with only corticoid and two were treated by both corticoid and cyclophosphamide.

DISCUSSION

In children, SLE is diagnosed most commonly in the adolescent age group and rarely occurs before the age of 5 years [4] and these founding confirm our results.

We found that the mean age of our patients was 11.5 years, our result was comparable to those found by Taddio et al. (12.7± 3.1), Hiraki et al. (13.1± 3.17), Bader-Meunier et al. (11.5± 2.5) and Muzaffer et al. (10.5) [9-11, 13]. In addition, in our series the female to male ratio was 3.1. This result was similar to those found by Taddio et al., Hiraki et al., Bader-Meunier et al. and Mondal et al., but different to the F/M ratio (14) found by Muzaffer et al. [9-11, 13, 20] (Table 5). This fluctuation of results could be due to the range of age. In fact, the range in our study was 9 months to 15 years, but it was 5 to 18 years in Muzaffer's study [13]. The youngest patient of our series who is also the youngest one in all the other series of SLE is 9 months old. In this patient, SLE was revealed by chronic lymphocytic meningitis which is a rare clinical manifestation of SLE and which appeared at the age of two months. It is important to mention that her mother had neither ANA nor clinical manifestations of SLE [25]. It has been demonstrated that SLE patients aged between 1-6 years had the highest incidence of neuropsychiatric system involvement [26].

In our study, we divided our patients in two groups; the first group includes the patients aged between 9 months and 12 years (45.9%) which correspond at the pre-puberty period, and the second group includes the patients who are older than 12 years which correspond at the age of puberty. This distinction between these two groups proves the role of hormonal factors including sexual hormones in which the production increase from puberty. In fact, the sexual hormones, especially estrogens, were implied in the induction of SLE witch explain the frequent incidence of SLE in women especially in genital activity period [27, 28]. These results were confirmed in our study. In fact, we have in the first group a sex-ratio F/M = 1.4 which explain that the incidence of SLE was almost equivalent between girls and boys.

However the sex-ratio in the second group was 9, it corresponds in the sex-ratio of the adult population in which the incidence of SLE was more frequent in female than in male.

Nevertheless, Bader-Meunier et al. found that the F/M ratio in the first group was 5.1 and it was 4.1 in the second group. This fluctuation could be due to the large series of SLE patients in the study of Bader-Meunier et al. [11].

Regarding to the clinical manifestations, in our study, anemia was the most common sign with a rate of 86.5% which is well above the rates recorded in other series. This difference could be explained, partly, by the fact that the results of other series (33.3%, 23%, 11.1%) found by Muzaffer et al., Hiraki et al. and Taddio et al. respectively [9, 10, 13] incorporate hemolytic anemia while our results include all types of anemia observed in the SLE, whether hemolytic or inflammatory.

Table 1. Patients demographic data

	Sex-ratio F/M	Mean age	Age range
SLE patients (n= 37)	28/9= 3.1	11.5 years	9 months-15 years
Age ≤ 12 years (n= 17)	10/7= 1.4	8.3 years	9 months-12 years
Age > 12 years (n= 20)	18/2= 9	14.2 years	13-15 years

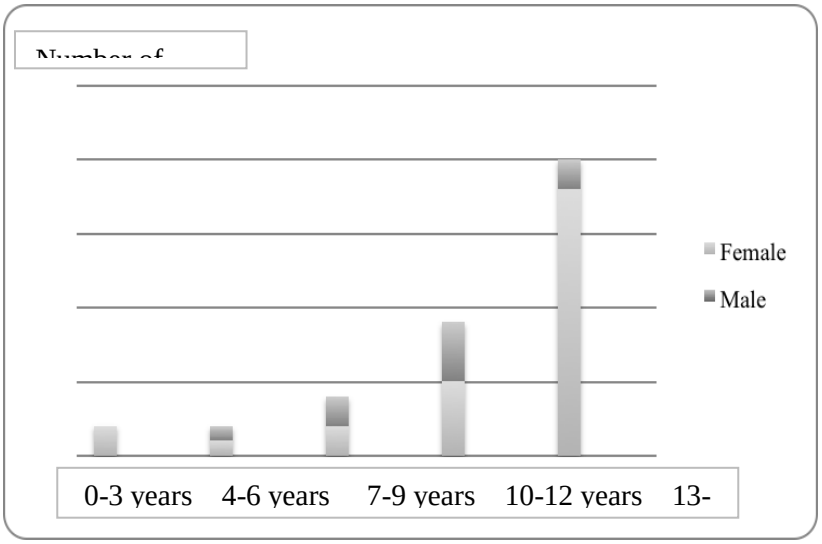

Figure 1. Distribution of SLE patients according to age and sex.

Table 2. Clinical and biological manifestations in 37 SLE patients.

	N	(%)
Dermatologic		
Malar rash	25	67.6%
Photosensitivity	16	43.2%
Oral ulcer	7	18.9%
Discoïd rash	5	13.5%
Joint		
Arthralgia	21	56.8%
Arthritis	17	45.9%
Serositis		
Pleuritis	4	10.8%
Pericarditis	3	8.1%
Renal		

Table 2. Cont.

Proteinuria[a]	27	73%
LN confirmed by renal biopsy	13	-
Class III	4	-
Class IV	7	-
Class V	2	-
Neuropsychiatric	5	13.5%
Haematologic	35	94.6%
Anemia[b]	32	86.5%
Leucopoenia[c]	14	37.8%
Thrombocytopenia[d]	12	32.4%

[a] 24-h protein excretion > 0.5 g/day
[b] Hb < 12g/dl
[c] WBC < 3.5x 109/l
[d] Thrombocytes < 150x109/l

Table 3. Biological findings of 37 SLE children on admission

Autoantibodies	N	%
ANA	37	100%
Anti-dsDNA	30	81.1%
Anti-Sm	21	56.8%
Anti-RNP	21	56.8%
Anti-SSA	16	43.2%
Anti-SSB	13	35.1%

Several studies have reported that children with SLE have often an aggressive clinical course and more frequent renal involvement as compared to adults [6, 7, 29]. In our study, the frequency of renal disease (73%) was similar to that found by Yalaoui et al. (75%) who had studied childhood SLE in the north of Tunisia and by Muzaffer et al. (73.3%) [12, 14], but a lower frequency has been found in other series [9, 20]. As it has been found in other series of childhood SLE, the class IV lupus nephritis (53.8%) was the most frequent one in our patients with proteuniria and who underwent renal biopsy [13, 15].

Cutaneous manifestations were malar rash (67.6%), photosensitivity (43.2%) and discoid rash (13.5%). Our results were similar to those found by Taddio et al. and Hiraki et al. [9, 10]. The frequency of arthritis in our study was 45.9%. This frequency was lower than that found by Hiraki et al. (61%) and Muzaffer et al. (73%). This fluctuation could be due to the number of patients and the interval of age chosen in each study [10, 13].

Table 4. Frequency of auto-antibodies in patients with lupus nephritis

	Anti-dsDNA	Anti-Sm	Anti-SSA	Anti-SSB	Anti-RNP
Patients with lupus nephritis **(n= 13)**	13/13 (100%)	9/13 (69.2%)	5/13 (38.5%)	6/13 (46.2%)	8/13 (61.5%)

Table 5. Comparison of clinical and biological features of our childhood SLE patients with other cohorts.

	Present study (n= 37)	Muzaffer et al. [13] (n=30)	Hiraki et al. [10] (N = 256)	Bader-Meunier et al. [11] (n=155)
F/M ratio	3.1	14	4.7	4.5
Mean age (range)	11.5± 3.8 (1-15)	10.5 (5-18)	13.1 ±3.17 (3-18)	11.5±2.5 (1.5-16)
Malar rash	25 (67.6%)	14 (47%)	155 (61%)	60 (39%)
Photosensitivity	16 (43.2%)	-	44 (17%)	20 (13%)
Oral ulcer	7 (18.9%)	1 (3.3%)	55 (21%)	16 (10.5%)
Discoid rash	5 (13.5%)	1 (3.3%)	-	10 (6.5%)
Arthritis	17 (45.9%)	22 (73%)	157 (61%)	-
Pleuritis	4 (10.8%)	2 (6.7%)	30 (12%)	-
Pericarditis	3 (8.1%)	3 (10%)	30 (12%)	-
Proteuniria	27 (73%)	22 (73.3%)	95 (37%) LN	81 (50%)
Neuropsychiatric	5 (13.5%)	9 (30%)	14 (35%)	-
Anemia	32 (86.5%)	65%	58 (23%)	42 (27%)
Leucopenia	14 (37.8%)	33%	73 (29%)	55 (35%)
Thrombocytopenia	12 (32.4%)	13%	75 (29%)	44 (28%)
ANA	37 (100%)	30 (100%)	256 (100%)	-
Anti-dsDNA	30 (81.1%)	(90%)	184 (72%)	144 (93%)
Anti-Sm	21 (56.8%)	-	88 (34%)	33 (32%)
Anti-RNP	21 (56.8%)	-	68 (27%)	36 (35%)
Anti-SSA	16 (43.2%)	-	69 (27%)	34 (33%)
Anti-SSB	13 (35.1%)	-	34 (13%)	20 (19%)

Pleuritis, pericarditis, oral ulcer and neuropsychiatric manifestations were rare in our study. These results were similar to those found by Muzaffer et al. [13].

The presence of ANA in the serum of our patients was the most constant biological sign; in fact it was detected in all patients (100%). The high frequency of ANA was found also in many other studies. In fact, Muzaffer et al., Hiraki et al., Yalaoui et al. and Taddio et al. found frequencies of 100%, 100%, 100% and 96% respectively [9, 10, 13, 15]. These results confirm the importance of the detection of ANA despite their low specificity in pediatric SLE [30]. Anti-dsDNA and anti-Sm antibodies are more specific for SLE. The frequency of anti-dsDNA antibodies in our series was 81.1% which was similar with the frequencies found by Muzaffer et al. (90%), Taddio et al. (90%), Hiraki et al.

(72%) and Yalaoui et al. (75%) [9, 10, 13, 15]. However, the frequency of anti-Sm antibodies in our series (56.8%) was higher than that found by Hiraki et al. (34%), Bader-Meunier et al. (32%) and Taddio et al. (35%) [9-11]. This fluctuation in results could be due to the different ethnics and origins of patients in these studies. In addition, this high frequency of anti-Sm antibodies was found in other Tunisian studies [22, 31]. In spite of the low specificity of anti-SSA, anti-SSB and anti-RNP antibodies in SLE, these antibodies had a high frequency in our study when compared with others. In fact, the frequency of anti-SSA antibodies in our series was 43.2% compared with 27% in the study of Hiraki et al., 33% in the study of Bader-Meunier et al. and 34% in the study of Taddio et al. [9-11]. The frequency of anti-SSB antibodies in our study was 35.1%, however, Hiraki et al. found 13%, Bader-Meunier et al. 20% and Taddio et al. 22% [9-11]. The frequency of anti-RNP antibodies in our series was 56.8%, while, it was 27% in the study of Hiraki et al. and 35% in the study of Bader-Meunier et al. [10, 11].

In conclusion, this study had shown that the most common clinical features were anemia, proteinuria and malar rash. SLE should be a prominent diagnostic consideration in paediatric patients.

ACKNOWLEDGEMENTS

This study is supported by Unité de recherche : Auto-immunité et Allergie (03/UR/07-02), Faculté de Pharmacie de Monastir, Tunisia.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest

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