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Medicine

« Autoantibodies and Systemic Lupus Erythematosus in a Moroccan Population »

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Abstract **Original Research Article**

Introduction: Systemic lupus erythematosus is characterized by various autoantibodies which prevalence and clinical significance vary among populations. The aim of our research is to study the immunological profile of autoantibodies in Moroccan population with lupus. ***Patients and methods:*** Seventy-seven patients with lupus meeting at least four criteria of the 1997 ACR had an ANA screening by indirect immunofluorescence method (IIF) on HEp-2 substrate (Kallstad, Biorad, threshold = 1: 160), followed by the identification of specific anti-DNAn antibodies (Aeskulisa, threshold: 16 IU / ml), anti-SSA, SSB, Sm, RNP, Nucleosomes, Histones [ELISA (ENA profile, Biorad) Immuno-Dot (D-Tek, Aesku)] and anti-phospholipid (APL-ELISA, DRG threshold: 10 IU / ml). ***Results:*** The mean age of the patients was 37.1 ± 14.13 with female predominance (Sex ratio M / F: 15.7). The clinical manifestations of SLE were dominated by rheumatological (80.6%), dermatologic (76.1%), renal (58.2%), respiratory (34.3%) neurological (28.3%) and cardiac (26.7%) symptoms. The ANA were found in all patients, anti-DNAn in 74.6%, associated with anti-nucleosome Ab and anti-histone in 58.5 and 36.5% of cases respectively. The SSA, Sm, RNP and SSB specificities were noted in 47.8; 37.3; 32.8% and 26.9% of cases respectively, and 19.4% of cases had Antiphospholipids Abs. A statistically significant association was established between anti-DNAn, anti-Sm and anti-RNP with renal impairment (p = 0.0007), pleurisy (p = 0.033) and Raynaud's phenomenon (p = 0.022) respectively. ***Conclusion:*** The data in our series show a particularly high level of anti-DNAn Ab and anti-SSA, with a correlation of anti-Sm Ab with pleurisy and anti-RNP with Raynaud's phenomenon. These results underline the interest of these markers in the clinico-immunological characterization of SLE.

Keywords: systemic lupus erythematosus, autoantibodies, immuno-clinical profile, Morocco.

INTRODUCTION

Systemic lupus erythematosus (SLE) is an autoimmune disease. Its etiopathogenic determinism involves genetic, endocrine, immunological and environmental factors [1, 2]. From a biological point of view, it is characterized by the production of multiple autoantibodies, most of them are directed against some components of the nucleus such as nucleic acids and nucleoproteins (DNA, histones and nucleosomes) and soluble nuclear antigens (Sm, RNP, SSA, SSB) [3,4]. These autoantibodies are biological markers of great diagnostic value and they have good significance in the prognosis and evolution assessment [5, 6-8]. According the ethnic origin of individuals, significant variations in clinical and immunobiological expression of the disease are observed [9, 10]. In Morocco, the SLE has been the subject of several studies, but few have focused on the prevalence of different autoantibodies and their clinical significance. The aim of our work was to determine the immunological profile of autoantibodies in patients with lupus and to study the clinico-biological characteristics of lupus in Moroccan adult population.

PATIENTS AND METHODS

This is a descriptive cross-sectional study of 67 lupus patients collected between 2012 and 2014 from the departments of internal medicine, nephrology, dermatology and rheumatology. Clinical data were collected using a questionnaire including sociodemographic and clinico-biological parameters. Patients in this study met at least four criteria from the American College of Rheumatology (ACR) [11].

The immunobiological investigation consisted on the search of antinuclear antibodies (ANA), carried out by Indirect immunofluorescence technique (IIF) on Hep2 cells (Kallstad slides, Biorad, threshold = 1: 160), of native anti-DNA antibodies using an ELISA

immunoenzymatic technique (Aeskulisa-dsDNA, threshold = 16 IU / ml), supplemented in case of positivity by IIF on Crithidia Luciliae substrate (Biorad, threshold = 1: 10).

The statistical data analysis was done by Epi software Info version 6 and was used to research associations between different autoantibodies and clinical manifestations. The significance of the results was retained for values of p <0.05.

RESULTS

Mean age of at the time of diagnosis was 37.1 ± 14.13, with extremes ranging from 18 to 69 years. The majority of patients were female (94%), with sex ratio F/M = 15.7. Clinical feature of the disease was dominated by rheumatologic manifestations, observed in 80.6% (n = 54) of patients (Table-1). These were arthralgia without arthritis in 37 cases (55.2%) and arthritis in 17 cases (25.4%). Mucocutaneous involvement was observed in 76.1% (n = 51) of the cases, dominated by photosensitivity (44.8%), alopecia (38.8%), malar rash (37.3%) and Raynaud's syndrome (23.9%). These manifestations found sole or associated with each other (Figure-1).

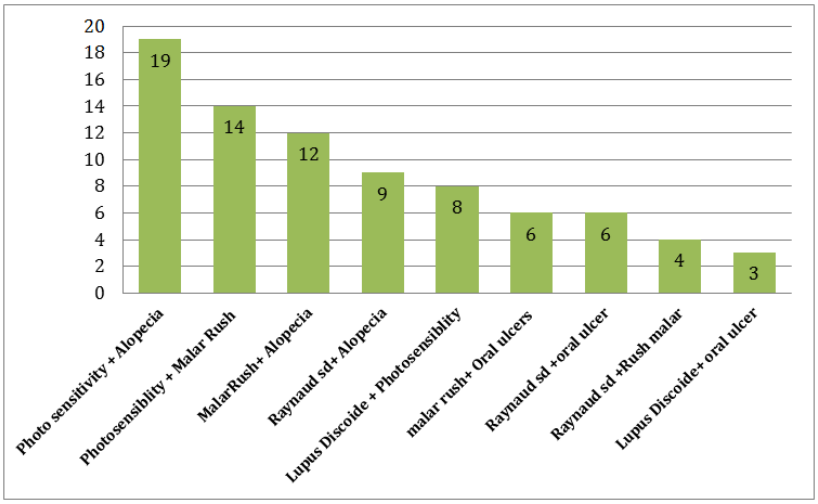

Fig-1: Distribution of main clinical associations in cutaneous and mucosal involvement R: Rash; Sd: Syndrome;

Renal involvement was found in 58.2% of cases (n = 39). For the pleuro-pulmonary involvement, pleurisy and interstitial lung disease were the most common and accounted for 25.4% (n = 17) and 8.9% (n = 6) cases, respectively. Cardiac involvement in 18 patients (26.7%) was dominated by lupus pericarditis (n = 13), associated with pleurisy in 9 cases and myocarditis in 3 cases. We noted two cases of vascular thrombosis, one case of deep vein thrombosis of the lower limb and one case of radial artery thrombosis. Neurologic involvement was noted in 28.3% of patients (n = 19) of whom 11 (16.4%) had central nervous system involvement and 8 (11.9%) had peripheral nervous system involvement.

Biologically, 86.6% of patients had anemia (74.6%, n = 50), followed by lymphopenia (68.6%, n = 46), leukopenia (37.3%, n = 25), thrombocytopenia (29.8%, n = 20) and neutropenia (11.9%, n = 8). Only two patients had hemolytic anemia. An inflammatory syndrome was found in 56 patients, defined by an acceleration of erythrocyte sedimentation rate (ESR) (83.6% of cases) and an increase in CRP (37.3% of cases). Among patients in our series, 17 (25.4%) had another autoimmune disease including 10 cases of Sjögren-Sjögren syndrome (SGS), 5 cases of antiphospholipid syndrome, and 2 cases of systemic sclerosis.

The frequency of auto-Ab sought during our study is reported in Table-1. The ANA search in IIF test was positive in all patients, showing Mixed Speckled/Homogeneous (MS/H) in 41.8% (n = 28), homogeneous (22.4%, n = 15), speckled (20.9%, n = 14), spotted-nucleolar (8.9%, n = 6) and homogeneous-speckled-nucleolar (6%, n = 4). Anti-DNAn Ab were found in 74.6% of cases (n = 50).

Table-1: Clinico-biological features of patients in our series

	n	%
Sociodemographic data		
Women	63	94
Man	4	6
Average age	37,1±14,13	-
Age at the time of diagnosis		
≤ 20 years	4	6
20 <age ≤ 40	45	67,2
40 <age ≤ 60	10	14,9
> 60 years	8	11,9
Clinical manifestations		
Hematological involvement	58	86,6
Rheumatological involvement	54	80,6
Dermatological involvement	51	76,1
Renal involvement	39	58,2
Pleuropulmonary involvement	23	34,3
Neurological involvement	19	28,3
Cardiaque involvement	18	26,9
Global immunological profile		
ANA	67	100
anti-DNAn Ab	50	74,6
anti-Sm Ab	25	37,3
anti-RNP Ab	22	32,8
anti-SSA Ab	32	47,8
anti-SSB Ab	18	26,9
APL	13	19,4

Anti-nucleosome Ab and anti-histone were positive in 58.2% (n = 39) and 37.3% (n = 25) cases, respectively. Positivity of anti-nucleosome antibodies and anti-histone was associated with anti-DNAn antibodies in 58.2% of cases (n = 39), and 2 patients had positive anti-nucleosome antibodies and anti-histone without anti-DNAn Ab (Table-2).

Table-2: Profile of anti-DNA antibodies and anti-nucleosome in our series

Antibodies Anti-	N	%
nucleosomes (+)	39	58,2
Histones (+)	25	37,3
DNA(+) nucleosomes (+) Histones (+)	21	31,3
DNA(+) nucleosomes (+) Histones (-)	16	23,8
DNA(-) nucleosomes (-) Histones (-)	15	22,3
DNA(+) nucleosomes (-) Hisones (-)	8	11,9
DNA(+) nucleosomes (-) Hisones (+)	2	2,9
DNA(-) nucleosomes (+) Histones (+)	2	2,9

Anti-ENA Ab was present in 59.4% of patients, corresponding to anti-SSA, anti-Sm, anti-RNP and anti-SSB specificities in respectively 47.8%; 37.3%; 32.8%; and 26.9% of cases. The combination of anti-Sm Ab with anti-RNP on the one hand and anti-SSA Ab with anti-SSB on the other hand was noted in 28.3% (n = 19) and 26.9% (n = 18) respectively. Antiphospholipid Ab was positive in 19.4% of patients.

The analysis of auto-Ab profiles according to different clinical specificities (Table-3), showed a significant association between anti-DNAn Ab and renal impairment (p = 0.0007), between anti-Sm and pleurisy (p = 0.033) and between anti-RNP and Raynaud's phenomenon (p = 0.022).

On the other hand, we found a statistically significant association between anti-RNP Ab and articular involvement associated with hematological involvement (p = 0.04); between anti-Sm and anti-RNP Ab and renal impairment, associated with neuropsychiatric involvement and serositis (p = 0.014 and p = 0.005 respectively), and between anti-SSA Ab and dermatological involvement associated with joint involvement (p = 0.02) (table-4).

Table-3: Auto-Ab and Clinical manifestations Association during SLE in our series

	Anti-DNAn		Anti-Sm		Anti-RNP		Anti-SSA		Anti-SSB	
	positives	p	positives	p	positives	p	positives	p	positives	p
	43(86)	NS	22(88)	NS	21(95,4)	NS	28(87,5)	NS	17(94,4)	NS
Hematologic	40(80)	NS	18(72)	NS	17(77,3)	NS	25(78,1)	NS	14(77,8)	NS
involvement, n (%)	21(42)	NS	9(36)	NS	10(45,4)	NS	12(37,5)	NS	8(44,4)	NS
Anemia, any etiology	34(68)	NS	18(72)	NS	19 (86,4)	NS	23(71,9)	NS	15(83,3)	NS
leukopenia	5(10)	NS	3(12)	NS	3(13,6)	NS	6(18,7)	NS	3(16,7)	NS
lymphopenia										
neutropenia										
Joint involvement, n (%)	43(86)	NS	20(80)	NS	19(86,4)	NS	25(78,1)	NS	15(83,3)	NS
	38(70)	NS	19 (76)	NS	17(77,3)	NS	26(81,2)	NS	14(93,3)	NS
Dermatological	22(44)	NS	12(48)	NS	10(45,4)	NS	15(46,9)	NS	8(44,4)	NS
involvement, n (%)	18(32,7)	NS	9(36)	NS	9(40,9)	NS	13(40,6)	NS	8(44,4)	NS
Photosensitivity	19 (38)	NS	11(44)	NS	10(45,4)	NS	13(40,6)	NS	7(87,5)	NS
Alopecia	7(14)	NS	3(12)	NS	2(9,1)	NS	2(6,2)	NS	1(5,5)	NS
Malar Rash	8(16)	NS	3(12)	NS	2(9,1)	NS	5(15,6)	NS	3(16,6)	NS
Discoid lupus	10(20)	NS	6(24)	NS	9(40,9)	**0,022**	8(25)	NS	3(16,6)	NS
Oral ulcerations										
Phenomenon of										
Raynaud										
Renal involvement, n (%)	35(70)	**0,000 7**	14(48)	NS	13(59,1)	NS	18(56,2)	NS	11(61,1)	NS
Neurological involvement (%)	16(32)	NS	6(24)	NS	8(36,4)	NS	9(28,1)	NS	3(16,6)	NS
	18(36)	NS	11(44)	NS	10(45,4)	NS	11(34,8)	NS	6(33,3)	NS
serositis, n (%)	14(28)	NS	10(40)	**0,033**	8(36,4)	NS	9(28,1)	NS	5(27,8)	NS
Pleurisy pericarditis	12(24)	NS	7(28)	NS	6(27,3)	NS	5(15,6)	NS	3(16,6)	NS

a: ACR Criteria; NS: not significant

Table-4: Study of Auto-Ab profiles according to clinical associations observed in our patients

	Anti-DNAn n(%)		Anti-Sm n(%)		Anti-RNP n(%)		Anti-SSA n(%)		Anti-SSB n(%)	
	positives	p	positives	p	positives	p	positives	p	positives	p
haematological + articular (n=47)	37(74)	NS	18(72)	NS	19(86,4)	**0,04**	23(71,8)	NS	15(83,3)	NS
haematological + Dermatological (n=45)	31(62)	NS	18(72)	NS	17(77,3)	NS	24(75)	NS	14(77,8)	NS
haematological + Renal (n=35)	29(58)	NS	12(48)	NS	10(45,4)	NS	17(53,1)	NS	11(61,1)	NS
articular + Dermatological (n=43)	31(62)	NS	16(64)	NS	14(63,6)	NS	16(50)	**0,02**	10(55,5)	NS
articular + Renal (n=34)	30(60)	0,001	11(44)	NS	9(40,9)	NS	15(46,9)	NS	10(55,5)	NS
articular + Neurological (n=19)	15(30)	NS	7(28)	NS	8(36,4)	NS	9(28,1)	NS	3(16,7)	NS
Dermatological + Renal (n=29)	27(54)	0,002	10(40)	NS	8(36,4)	NS	13(40,6)	NS	9(50)	NS
Dermatological + hematological+ articular (n= 36)	26(52)	NS	14(56)	NS	15(68,2)	NS	20(62,5)	NS	12(66,6)	NS
Dermatological + serositis [a] (n=14)	13(26)	NS	8(32)	NS	7(31,8)	NS	8(25)	NS	3(16,7)	NS
Renal + Neurological (n=12)	12(24)	0,025	6(24)	NS	6(27,3)	NS	5(15,6)	NS	2(11,1)	NS
Renal + serositis [a] (n=18)	16(32)	NS	10(40)	NS	9(40,9)	NS	10(31,2)	NS	6(33,3)	NS
Renal + Neurological + serositis [a] (n=6)	6(12)	NS	5(20)	**0,014**	5(22,7)	**0,005**	4(12,5)	NS	1(5,5)	NS

a: ACR Criteria; NS: not significant

DISCUSSION

SLE is classically a disease of young woman; the average age of the patients in our study (37.1 years) is in agreement with the main series of the literature which report averages ranging from 25 to 41 years [13, 14-18]. Female predominance is reported in several series, with a sex ratio F / H of 17 in Brazil [19], 16 in Senegal [20], 10 in Europe [21], 11.3 in Tunisia [18] , 11.29 in China [16] and 15.7 in our series. Our study also confirms the clinical polymorphism widely described in the literature [2, 18, 20, 22]. Immunologically, the pattern of auto-Ab during this condition varies significantly by region, country and also by ethnicity (Table-5).

Table-5: Frequency of autoantibodies during SLE according to series

Auto-Ab	Africa			Europe		Latin America			Asia			USA		Our séries
	Tunisia [9, 20, 23]	Senegal	SA	Spain [21, 24]	Finland	White [25]	Métis	ALA	China [26, 28, 27]	India	Dubai	AA [29]	White	
ANA (%)	97,6	85,7	98.2	96	96,1	99.4	95.9	99.3	96.7	98	98	-	-	100
DNAn(%)	75	62,5	66.7	78	44,2	67.2	74.6	69.5	75.6	55	88.7	58	50	74,6
Sm (%)	36,9	69,6	44.2	10	12	47.1	48.8	50	30.3	29	19.7	24	10	37,3
RNP (%)	32,1	68,7	65.5	13	22,7	49.3	54.2	52.2	46.3	-	40.4	36	12	32 ,8
SSA (%)	54,8	54,5	60.5	25	61,8	50.2	46.5	47.5	66	34	52.3	28	18	47,8
SSB (%)	14,3	36,3	28.4	19	23,6	26.1	31.4	35	23.8	14	19.8	12	7	26,9
APL (%)	45,2	-	-	24	-	50.6	55	48.7	-	34,5	25.3	42	46	19,4

SA: South Africa, ALA: Afro-Latin American, AA: African-American

ANAs are almost-constant biological marker during SLE; found in all of our patients, their frequency varies between 85 and 100% according to the series [20, 21, 26, 28, 30]. Unlike many series of literature where the homogeneous aspect of the ANAs remains most frequently found during the SLE [31], the mixed homogeneous-speckled aspect predominates in our study. The anti-DNAn Ab, which specificity for the SLE is better defined, varies in frequency from 29 to 98%, it is 74.6% in our series [9, 21, 25, 26, 28, 29, 32, 33]. This rate is reasonably high compared to that described in North American (50%) [29], Finnish (44.2%) [24] and Indian (55%) series [27]. On the other hand, it remains lower than that reported in the United Arab Emirates (88.7%) [28]. In agreement with the data in our series, several studies have reported frequent association with renal impairment [22, 23, 26, 34, 35]. In addition to renal involvement, Thompson *et al*. [36] reported that patients with anti-DNAn were more likely to have malar rash, hypocomplementemia, and hematologic involvement. The data in our series is partly consistent with this last series, since anti-DNAn antibodies were statistically significant in the renal involvement associated with cutaneous involvement, whereas the latter was not statistically significant during the combination of renal and hematological involvement.

Moreover, it is commonly known that anti-DNA Ab is also correlated with the activity of lupus disease, and that a high rate of these usually precedes an exacerbation of SLE, similarly, the persistence of high rates signifies a lupus nephropathy [6, 37]. Thus, monitoring often predicts relapse in SLE patients [9, 38-40]. Anti-nucleosome antibodies are a good marker of SLE, their frequency varies between 56 to 88% [41, 42], it is 58,2% in our patients. Among Lupus patients without detectable anti-DNAn Ab, 10 to 65% have anti-nucleosome Ab [22, 42-44]. In our study, they were mutually exclusive (without anti-DNAn Ab) in 2 patients (2.9%), but associated with anti-histone Ab. Their research seems relevant whenever the clinical examination is suggestive of SLE and that ANA research is anti-chromatin positive (homogeneous with chromosome labeling on mitotic cells) without anti-DNAn Ab [5, 9, 44]. However, there is some ambiguity about the specificity of anti-nucleosome Abs for SLE: Amoura *et al*. reported a 45% rate in scleroderma and mixed connective tissue disease [46]. Other studies report a frequency less than 5% in other autoimmune diseases [47]. On the other hand, the prognostic value of anti-nucleosome Ab, especially for lupus nephropathy, is illustrated by several studies [9, 39, 40, 45, 48]. Considered correlated with disease activity, their research appears to be of real interest during follow-up, particularly in lupus patients without anti-DNA-Ab [9, 45, 48, 49]. The rate of anti-histone antibodies in our series (37.3%) is comparable to that described in Tunisia, 44% [9] and in India, 35% [50], but remains significantly higher than that observed in Belgium, 28.5%. % [32] and Mexico, 15% [45]. Apart from the very particular case of induced lupus, their research has very little value in clinical practice during SLE [4, 51]. Anti-Sm Ab is one of the biological criteria for diagnosis to SLE. They are not very sensitive but generally very specific of the disease, they are often associated with anti-U1 RNP Ab [4, 52, 53]. Their prevalence varies during SLE according to the populations studied but especially according to the techniques used. Indeed, their sensitivity is particularly high in black race, about 50% [23, 54], whereas in Caucasian populations they are found in only 10 to 20% [21,53]. The sensitivity of 37.3% observed in our series and 36.9% in Tunisia [9] seems to define the Maghreb populations as intermediate. According to several authors, the presence of anti-Sm Ab is significantly associated with malar rash [26, 34, 55], leukopenia [26,56], and serous involvement [26,57,58]. This last observation is also confirmed by the significant association of anti-Sm Ab in pleurisy in our patients.

Unlike Tikly23, Yasuma59 and Hirohata60 *et al.* who found a significant association between these Ab and neuropsychiatric involvement.

Markers of high specificity with regard to mixed connective tissue where they are constantly and strongly present [3,4], the anti-RNP Ab are also described during the course of the SLE with a frequency varying from 12 to 68,7 % [9,20,21,23,24,26,29]. In our study, they are present in 32.8% of patients and the correlation that we established with Raynaud's phenomenon is also found in several studies [32, 53, 57, 58].

Anti-SSA Ab was detected with a fairly high frequency (47.8%) in our patients, consistent with numerous series of the literature that report a frequency varies from 25 to 66% [18, 20, 21, 23, 25, 26]. Indeed, anti-SSA Ab have a strong predictive value for the diagnosis of SLE, particularly for ANA-positive patients but without anti-DNA or anti-Sm [61]. Peene *et al*. by analyzing the clinical diagnosis of 181 patients with anti-SSA Ab and / or anti-SSB in their serum, confirmed this finding, since 80% of patients with only anti-SSA proved to have lupus [62]. We found that anti-SSA Ab was statistically significant in patients with both dermatologic and joint involvement, consistent with the findings of Diallo *et al.* who found a significant association between these two parameters [20]. In addition, studies have established the association of these Abs with renal involvement [23, 34, 60, 63], malar rash [23, 34], photosensitivity [58,64], cutaneous lupus [34,65] and interstitial lung disease [34,66,67].

Anti-SSB Ab are particularly present during primary Sjogren's Gojron Syndrome with a prevalence ranging from 30 to 70% [3,8], whereas during SLE, the authors report a frequency varying between 7 and 36% [9, 20,23,25,28,29], including that of our study (26.9%).Among SSB-positive patients in our series, one-third had SLE associated with lupus disease, which allows us to assume that other patients will develop clinical manifestations of dry syndrome in the medium to long term.

Commonly associated with venous or arterial thrombotic events or repeated abortions in lupus patients [68, 69], the presence of APLs during SLE varies widely between series, ranging from 20 to 87% [9, 18, 21, 22, 27, 38], with an average frequency of 20 to 40% [5,69].

Finally, despite its originality and its medico-scientific benefits, our study would certainly have some pitfalls. Indeed, in the case of a cross-sectional study, the establishment of a better clinico-immunological correlation of the different markers studied requires the consideration of different clinical stages of the disease which may be accompanied by the appearance or disappearance of auto-Ab. Such an approach would require a longitudinal study.

CONCLUSION

Our study confirms the predominance of women, the early age of patients at the beginning of the disease and the clinico-biological polymorphism of LES. The high prevalence of anti-SSA Ab in our series, gives them a significant predictive value for the diagnosis of SLE. Also, the frequency of anti-Sm Ab in the Maghreb populations remains intermediate compared to that considered high noted in black race and low recorded in Caucasian populations. Moreover, clinico-immunological associations found in our series generally agree with different series in literature. These data highlight the importance of these autoantibodies and their place both in the diagnostic approach and in the characterization, therefore, in better management of lupus disease.

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