Original Paper

Immunological Profile in Patients with Lupus Nephritis and Correlations with the Histological Pattern

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ABSTRACT **Background.** Lupus nephritis (LN) is a common manifestation in patients with systemic lupus erythematosus (SLE). Certain serum autoantibodies are associated with the presence of nephritis**. Objective.** The aim of the study is to describe and analyse the immunological antibody profile associated with the development of nephritis in patients with systemic lupus erythematosus and to find possible correlations with the histological pattern. **Patients and methods**. We designed a retrospective case control study of 61 patients with biopsy proven LN and 110 patients with SLE without LN. We used standard methods for laboratory testing of anti-dsDNA, anti-ENA and anti-phospholipid antibodies. **Results.** Patients with LN were significantly younger at the time of diagnosis ((26.4 (6.4) years versus 35.2 (10.6) years; p<0.001) A higher frequency of anti-dsDNA, anti-Sm and LA was seen in the group with nephritis (p=0.002; p=0.005; p=0.0001).There were no significant correlations with gender, or the tipe of WHO histological classes identified in patients with lupus nephritis compared with those without renal disease. **Conclusions**. The factors associated with LN outlined in the current study are the presence of anti-dsDNA, anti-Sm antibodies and of LA.

KEY WORDS *lupus nephritis, autoantibody profile, renal biopsy*

Introduction

Systemic lupus erythematosus (SLE) is a heterogeneous autoimmune dissease, of uncertain ethiology, with numerosus patterns of clinical manifestations due to the production of autoantibodies which makes a complex immunological profile; the outcome is fluctuating, with remmisions and flares, and the prognosis is various, according to the global disease. Due to numerous patterns of clinical manifestations, it represents the prototype of antoimmune diseases.

Renal disease in SLE occurs in up to 40-75% of patients, most often within five years of disease onset, and is considered one of the strongest predictors of a unfavourable outcome, thus being one of the most serious clinical manifestations that eventually affects about 50% of patients some time in the course of their illness (1).

Renal glomeruli represent the most involved structure, presenting as lupus nephritis (LN). The pathogenic events that generate the histopathological changes in the glomeruli are initiated by the immune complex formation and deposition – cirrculating or in situ – in the mesangium, subepithelial or subendothelial. Regarding in situ formation of immune complexes the role of anti-dsDNA antibodies of the lupic kidney is essential, by targeting polinucleotides, ribonuclotides and phospholipids. This type of polireactivity represents a distinctive intervention of the nephritigen anti-dsDNA antibodies of forming in situ immune complexes at renal level and now there is relevant evidence confirming the pathogenic role for DNA- anti-DNA immune complexes in LN (2). Also, antigen - antibody reactions involving anti-Ro, anti-La, anti-Sm, anti-RNP (ENA), anti-ribosomal P, or anti-phospholipid antibodies may also contribute to the pathogenesis of nephritis but the evidence is still controversial.

Objectives

The aim of the study is to describe and analyse the immunological antibody profile associated with the development of nephritis in patients with systemic lupus erythematosus from our regional community over the last 10 years, and to find possible correlations with the histological pattern revealed by the renal biopsy.

Patients and methods

We designed a retrospective study comparing 61 patients with biopsy proven LN with 110 SLE patients without LN. All patients enrolled in the current study were classified with SLE according to the revised American College of Rheumatology (ACR) criteria (3).

We considered the first appearance of clinical manifestations the age of the disease onset as shown in the medical records registered over time, and the time of the renal disease debut the date of the first biopsy. We also calculated the evolvement time of renal disease as the difference between the time of diagnosis and the time of first biopsy.

The immunological profile in these patients assumed various lupus specific and non-specific antibody detection. Antibody assessement was performed as follows: anti-dsDNA antibodies by radioimmunoassay (Farr assay), antibodies to ENA present in SLE (anti-Ro, anti-La, anti-Sm, anti-RNP) by countercurrent immuno-electrophoresis (CIE) and aCL by ELISA. The presence of lupus anticoagulant (LA) was assessed by measuring the activated partial thromboplastin time and the dilute Russell viper venom and patients were conssidered positive for aCL/LA when the results of these determinations were positive on at least two separate occasions, at least six weeks apart, according to the criteria under current use (4).

All renal biopsies recorded in the pathology department were performed by a certified histopathologist specialising in renal pathology and the biopsy specimens were classified according to the World Health Organisation (WHO) criteria (5): minimal mesangial lupus nephritis (class I), mesangial proliferative lupus nephritis (class II), focal proliferative lupus nephritis (III), diffuse proliferative lupus nephritis (IV), membranous lupus nephritis (V) and advanced sclerotic lupus nephritis (VI).

Results

The data analysis revealed as expected, the predominance of the disease in females in both groups (86.66% versus 86.36%), without any significant statistic difference regarding gender distribution in patients with or without lupus nephritis (Table 1). The same lack of significant statistical difference was noticed when comparing disease duration (118.5 (2.4) months vs. 120.6 (1.5) months) recorded in the medical records (Table 1).

An interesting finding is that patients with lupus nephritis were significantly younger at the time of SLE diagnosis than the control group of patients without renal disease (26.4 (6.4) years versus 35.2 (10.6) years; p<0.001) (Table 1).

The two groups showed a different immunological profile, as patients with lupus nephritis expressed a higher frequency of anti-dsDNA, anti-Sm, anti-RNP antibodies and of LA, compared with those patients without renal disease (Tables 2,3). The study failed in finding any associations between the age at SLE diagnosis and the time to the appearance of renal disease (r=0.08).

Table 1. Demoghraphic characteristics of patients with or without lupus nephritis.

Characteristic	SLE with nephritis (n=61)	SLE without nephritis (n=110)	p
Age at diagnosis	26.4 (6.4)	35.2 (10.6)	<0.001
Gender (F/M)	52/9	95/15	NS
Time of survey (months)	118.5 (2.4)	120.6 (1.5)	NS

Table 2: Immunological profile in patients with or without lupus nephritis.

Antibodies	SLE with nephritis + (%)/- (%)	SLE without nephritis +(%)/- (%)	p	OR
ANA	59(96.7%) 2(3.3%)	108(98.25) 2(1.8%)	NS	1.86
dsDNA	40(65.5%) 21(34.5%)	57(51.8%) 53(48.2%)	0.002	2.06
RNP	21(34.5%) 40(65.5%)	22(20%) 88(80%)	0.0001	2.05
Sm	15(24.6%) 46(75.4%)	10(9.1%) 100(81.9%)	0.0001	3.25
Ro	23(37.7%) 38(62.3%)	40(36.3%) 70(63.7%)	NS	1.03
La	6(9.8%) 55(90.2%)	19(17.2%) 91(82.8%)	0.047	0.49
aCL IgG	19(31.1%) 42(68.9%)	26(23.6%) 84(76.4%)	NS	1.42
aCL IgM	6(9.8%) 55(90.2%)	15(13.6%) 95(86.4%)	NS	0.67
LA	24(31.1%) 37(58.9%)	28(25.4%) 82(74.6%)	0.01	1.85

Table 3: Immunological profile and the class of nephritis in patients with SLE

Characteristics	class II no (%)	class III no (%)	class IV no (%)	class V no (%)	p
Age at diagnosis	21.6	25.5	25.2	27.3	NS
Gender (F/M)	5(100)	14(93.3)/ 1(6.7)	22(95.6)/ 1(4.4)	16(88.8)/ 2(11.2)	NS
DNAds (+/-)	3(60%)/ 2(40%)	11(73.3)/ 4(26.7)	16(69.5)/ 7(30.5)	10(55.5)/ 8(45.5)	NS
RNP(+/-)	1(20)/ 4(80)	4(26.6)/ 11(73.4)	8(34.8)/ 15(65.2)	8(44.4)/ 10(55.6)	NS
Sm(+/-)	1(20)/ 4(80)	3(20)/ 12(80)	6(26)/ 17(74)	15(83.3)/ 3(16.7)	NS
Ro(+/-)	1(20)/ 4(80)	9(60)/ 6(40)	7(30.4)/ 16(69.6)	6(33.3)/ 12(66.7)	NS
La(+/-)	0/ 5(100)	2(13.3)/ 13(96.7)	2(8.7)/ 21(91.3)	2(11.1)/ 16(88.9)	NS
IgG aCL (+/-)	2(40)/ 3(60)	5(33.3)/ 10(66.7)	4(17.4)/ 19(82.6)	8(44.4)/ 10(56.6)	NS
IgM aCL (+/-)	1(20)/ 4(80)	2(13.3)/ 13(96.7)	2(8.7)/ 21(91.3)	1(5.5)/ 17(94.5)	NS
LA (+/-)	2(40)/ 3(60)	6(40)/ 9(60)	9(39.1)/ 14(60.9)	7(38.8)/ 11(61.2)	NS

The renal biopsy specimens of the analysed patients revealed the presence of four clases of the WHO classification, with the lack of the advanced sclerotic lupus nephritis and the nephritis with minimal changes. The most encountered type of

renal disease was the diffuse proliferative glomerulonephritis (class IV) in 23 patients, followed by the membranous lupus nephritis (class V) in 18 patients, the focal proliferative nephritis (class III) in 15 patients, and mesangial proliferative lupus nephritis (class II) in 5 patients (Table 3).

There were no differences regarding the gender or immunological profile and the histological class of nephritis identified on the biopsy samples (Table 3).

Disscution

The current study outlines that among the populations studied, in the group with lupus nephritis the patients were younger at the time of SLE diagnosis than in those without nephritis, as showen in previous research articles that have noted that nephropathy is less common in adult onset disease (6,7). There is still a lack of certainty regarding the different disease patterns connected to disease onset, but several theories have been suggested, such as demographic factors, genetic predisposition and a differnt behaviour of an aging immune system (8,9).

The clinical significance of autoantibodies and their profiling in renal disease has represented a continuous concern for several study groups, however, with a tremendous attention on the anti-dsDNA antibodies in the attempt to determine their role in disease pathogenesis as well as in the various subsets of the disease. As proven by several lupus nephritis trials (6,7,10), our study found that the presence of anti-dsDNA antibodies was a factor associated with the presence of nephritis, suggesting a prevalent role in the disease profile regarding the renal involvement.

The presence of LN in our study has been found to be uncommon in patients with both anti-Ro/SSA and anti-La/SSB antibodies, no significant correlation was seen in patients with anti-Ro antibodies alone, while a negative correlation was observed in patients with anti-La antibodies regarding the association of lupus nephritis.

There was a significantly higher proportion of RNP positive patients in our study group with lupus nephritis, although in literature anti-RNP antibodies have been reported to occur in lower frequency, except when associated with anti-Sm and anti-Ro autoantibodies.

We also found anti-Sm to be an important factor in the development of nephritis, as the differences between the two groups were statistically significant, observation supported by the data from literature that reports the presence of anti-Sm antibodies as well correrelated to renal disease especially when associated with the preesence of anti-dsDNA antibodies (11,12,13).

Our study also outlined the important role in the pathogenesis of renal disease of antiphospholipid antibodies, as it proved that the presence of LA was an independent factor for the development of lupus nephritis, although the role of antiphospholipid antibodies in the pathogenesis of LN is not clear in literature data (14,15).

Of interest is the importance of the current study in confirming earlier data concerning the lack of the correlation between the immunological profile in patients with systemic lupus erythematosus and histological class of nephritis (16).

Conclusions

In summary, the results of our study suggest that factors associated with LN in our group were younger age at SLE diagnosis, anti-dsDNA, anti-Sm antibodies and AL , as well as the lack of the correlation between the immunological profile in patients with systemic lupus erythematosus or gender with the histological class of nephritis.

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