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Comparison of lupus patients with early and late onset nephritis: a study in 71 patients from a single referral center

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Abstract

Background: Nephritis occurs frequently in systemic lupus erythematosus (SLE) and may worsen disease morbidity and mortality. Knowing all characteristics of this manifestation helps to a prompt recognition and treatment.

Aim: To compare the differences in clinical data, serological profile and treatment response of nephritis of early and late onset.

Methods: Retrospective study of 71 SLE patients with biopsy proven nephritis divided in early nephritis group (diagnosis of nephritis in the first 5 years of the disease) and late nephritis (diagnosis of nephritis after 5 years). Epidemiological, serological, clinical and treatment data were collected from charts and compared.

Results: In this sample, 70. 4% had early onset nephritis and 29.6% had late onset. No differences were noted in epidemiological, clinical, serological profile, SLICC and SLEDAI, except that late onset nephritis patients were older at nephritis diagnosis ($p = 0.01$). Regarding renal biopsy classification, C3 and C4 levels, serum creatinine, 24 h proteinuria and response rate to treatment the two groups were similar (p = NS). Patients with early onset had lower levels of hemoglobin at nephritis onset than those of late onset ($p = 0.02$).

Conclusions: Most of SLE patients had nephritis in the first 5 years of disease. No major differences were noted when disease profile or treatment outcome of early and late onset nephritis were compared.

Keywords: Systemic lupus Erythematosus, Nephritis, Treatment, Prognosis

Introduction

Renal involvement in systemic lupus erythematosus (SLE) is one of most common and feared manifestations of this disease as it is related to high morbidity and increased rate of mortality [1]. It has been estimated that almost half of adults and 80–90% of children with systemic lupus will develop kidney involvement [2] and that 10% of them will go into renal failure [3, 4].

Several factors may affect the prognosis in this context. Ethnic background is one of them; nephritis is more common and more severe in African, Asian and Latin American individuals [5]. Early age at lupus onset and male gender are other factors [6].

Lupus nephritis is more frequent in those with anti-dsDNA [7] and it is less common in those with discoid manifestations [8] and positivity for rheumatoid factor [9]. It usually occurs within the first years after diagnosis [10] although some patients do develop this complication later on. Few studies [11, 12] address to the characteristics of patients with late onset of nephritis that could allow an early identification and treatment.

Herein we studied systemic lupus patients with nephritis to see if there are differences in clinical, serologic profile and treatment response in patients to analyze those who develop this manifestation early (within the first 5 years) or later in the disease course.

Methods

This study was approved by the local Committee of Ethics in Research. It was a retrospective study that included patients with lupus nephritis from a single rheumatology outpatient clinic that attended for regular consultation during the period of 10 years. To be included patients should have SLE diagnosis after 16 years

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of age, nephritis proved by renal biopsy and received standard treatment for the renal involvement: induction with glucocorticoid, intravenous cyclophosphamide (0.5 to 1.0 g/m2/month for 6 months) or mophetyl mycophenolate (MMF) (2-3g/day - 6 months) and maintenance for at least 2 years with either azathioprine or MMF. Pregnant patients, those who did not complete the treatment and that received any other immunosuppressants were excluded. Clinical and serological data were collected from the charts. The clinical profile was considered in a cumulative manner and collected following the definition of the 1997 American College of Rheumatology revised criteria for the classification of Systemic Lupus Erythematosus [13]; secondary APS (antiphospholipid antibody syndrome) followed the 2006 modified APS criteria [14]. The autoantibodies tested in the serological profile were: anti-Ro/SS-A, anti-La/SS-B, anti-RNP, anti-Sm, anti-dsDNA, anticardiolipin (aCl) IgG, aCl IgM, LA (lupus anticoagulant), direct Coombs and rheumatoid factor (RF). Anti-Ro/SS-A, anti-La/SS-B, anti-RNP, anti-Sm, aCl-IgG, aCl-IgM were tested by ELISA (using ALKA and Orgentec Kits); anti-dsDNA, by immunofluorescence technique (IFT); the lupus anticoagulant, by screening test, the dRVVT (dilute Russell viper venom test) and confirmed by RVVT. Latex agglutination test (BioSystems) was used to search IgM RF and monoclonal anti human globulin Fresenius-Kabi-Brasil was used for the direct Coombs test.

Data on nephritis included: renal biopsy classification according to ISN/RPS (International Society of Nephrology/ Renal Pathology Society) [15], 24 h proteinuria, creatinine levels, creatinine clearance, values of serum complement fractions C3 and C4, anti-dsDNA positivity and hemoglobin (hb) levels just prior to induction treatment, and after 2 years of treatment. The time from the end of treatment until the first nephritis relapse was also collected.

To be considered as treatment responder patient should have had stabilization or improvement of renal function and reduction of proteinuria to less than 0.5 g / day and /or normal clearence or increase of only up to 10% without active sediment. To be considered as partially responders, they should show reduction of 50% of proteinuria with < 3 g / day and normal clearance or with alteration of up to 10% of the previous value [16]. Non-responders were those with deterioration of renal function after excluding causes such as sepsis, drugs, dehydration and renal vein thrombosis and / or increased proteinuria or non-reduction of proteinuria in order to fall into partial or total remission.

SLEDAI (Systemic Lupus Erythematosus disease activity) [17] and SLICC/ACR DI (Systemic Lupus International Collaborating Clinics/ American College of Rheumatology Damage Index) [18] were calculated in the beginning of the treatment and after 2 years.

Patients were divided in two groups, for comparison: (1) those with nephritis that initiated within the first 5 years after SLE diagnosis and classified as early nephritis group; (2) those with nephritis diagnosed more than 5 years after SLE diagnosis and classified as late nephritis group.

Data was collected in frequency and contingency tables. Data distribution was tested by the Shapiro Wilk test. Central tendency was expressed in mean and standard deviation or median and interquartile range (IQR) according to the distribution of studied data. Nominal data were compared by Fisher and chi-squared tests and the numeric, by U-Mann-Whitney and unpaired t tes, respectively. The software Medcalc 10.0 was used for calculations. The adopted significance was of 5%.

Results

a) **Description of studied sample and comparison of clinical and serological data:**
Seventy-one patients met the inclusion criteria: 50 (70. 4%) of them had early onset of nephritis and 21 (29.6%) had late onset. Table 1 shows the main characteristics of this group and the comparison between early and late onset nephritis groups.

b) **Comparison of renal involvement in early and late onset nephritis.**

The comparison between early and late onset nephritis is on Table 2. In this table it is possible to see that patients from the late nephritis group had a better hemoglobin level in the initial evaluation, showed tendency to recur earlier and had a positive anti-dsDNA more frequently than those in the early nephritis group. Otherwise the two groups had similar results.

We performed a logistic regression - with group of early or late onset as the dependent variable taking into account age, SLICC, SLEDAI and patients age and GNF class. We could not obtain any significance.

Studying only class III and class IV glomerulonephritis, no differences were noted in the remission rate at 1 year ($p = 0.72$) neither at 2 years ($p = 0.30$).

Discussion

Our results showed that almost 2/ 3 of lupus patients developed nephritis in the first 5 years after the diagnosis. This preference for early development of nephritis was already highlighted by Cameron [19] that emphasized that 25 to 50% of unselected patients with lupus have abnormalities of urine or renal function early in the course of disease. Also, in juvenile lupus up to 80% of patients developing lupus nephritis do it within the first 5 years from diagnosis [20]. The present sample had only adult SLE patients and the age at SLE diagnosis was similar in both groups, but patients in the early nephritis

Table 1 Comparative analysis of clinical and serological data in 71 patients with Systemic Lupus Erythematosus (SLE) with early and late onset nephritis

	Total sample *N* = 71	Early nephritis *N* = 50 (70. 4%)	Late nephritis *N* = 21 (29.6%)	P [a]
Ethnic background [b]	Caucasians 27 Afrodescendants 44	Caucasians 16 Afrodescendants 34	Caucasians 11 Afrodescendants 10	0.64
Median age at SLE diagnosis (years) (IQR)	26.0 (21.0–38.0)	27 (21-40.2)	26 (21.0–37.0)	0.67
Median age at nephritis diagnosis (years) (IQR)	30.0 (23.0–42.0)	27.5 (21. 7-41.0)	35 (29. 5-43.5)	0.01
Female gender	62 (87. 3%)	43 (84. 3%)	19 (90. 4%)	0.71
Tobaco exposure	8 (11.2%)	4 (9%)	4 (19.0%)	0.22
Malar rash	30 (42.2%)	20 (40%)	10 (47.6%)	0.55
Discoid lesions	2 (2.8%)	0	2 (9.5%)	0.08
Photossensitivity	48 (67.6%)	32 (64%)	16 (76.1%)	0.72
Oral ulcers	35 (49.2%)	24 (48%)	11 (52. 3%)	0.73
Articular involvement	60 (84.5%)	40 (80%)	20 (95.2%)	0.15
Serositis	18 (25. 3%)	15 (30%)	3 (14.2%)	0.23
Psychosis	1 (1. 4%)	0	1 (4.7%)	0.29
Convulsions	6 (8. 4%)	6 (12%)	0	0.16
Hemolytic anemia	8 (11. 4%)	7 (14.2%)	1 (4.7%)	0.42
Leukopenia	25 (35.2%)	15 (30%)	10 (47.6%)	0.15
Lymphocytopenia	15 (21.1%)	11 (22%)	4 (19.0%)	1.00
Thrombocytopenia	2 (2.8%)	1 (2%)	1 (4.7%)	0.50
Anti-Ro (SS-A)	26 (36.6%)	19 (38%)	7 (33. 3%)	0.70
Anti-La (SS-B)	10 (14.0%)	7 (14%)	3 (14.2%)	1.00
Anti-RNP	13 (18. 3%)	7 (14%)	6 (28.5%)	0.14
Anti-Sm	13 (18. 3%)	8 (16%)	5 (23.8%)	0.50
Positive Coombs	6 (8. 4%)	5 (10%)	1 (4.7%)	0.66
Rheumatoid factor	6 (8. 4%)	6 (12%)	0	0.16
Anticardiolipin IgG	1 (1. 4%)	1 (2%)	0	1.00
Anticardiolipin IgM	2 (2.8%)	2 (4%)	0	1.00
Lupus anticoagulante	5 (7.0%)	3 (6%)	2 (9.5%)	0.62
Antiphospholipid antibody syndrome	5 (7.0%)	3 (6%)	2 (9.5%)	0.62

[a] refers to early onset versus late onset; [b]- auto declared; *IQR* interquartile range, *n* number

group were younger at nephritis diagnosis. Unfortunately, no other clinical or serological differences could be noted between the two groups that could be associated to the nephritis onset. However our sample was small and may not have had enough strength to demonstrate any differences. It is worthwhile to note that in this sample there were 61.9% of class IV nephritis in the late onset compared to 50% in the early onset group and this data should be take into account to explain the tendency for early relapse in the late onset group. Relapse rate in class IV nephritis is more common [21].

Renal involvement in SLE is recognized as a major cause of high morbidity and mortality [22] and its prompt recognition and treatment is associated with better prognosis [23].

Regarding treatment, the rate of response was similar in both groups, although a tendency to early relapse was noticed in the late onset nephritis group, with no significance (Table 2). Considering this, patients with late onset nephritis should be treated as aggressively as those of early onset in order to prevent renal damage.

Contrary to our findings, Varela et al. [12] associated the delayed onset nephritis with the presence of antiphospholipid antibody syndrome (AAF). Our sample had only few cases of AAF that precluded a good observation of this aspect.

This study has some limitations: its retrospective design and the follow up of only 2 years. Another is that nephritis remission was judged only on clinical grounds. It is well known that lupus patients with nephritis may

Table 2 Comparative analysis of main characteristics and treatment response in Systemic Lupus Erythematosus (SLE) patients with early and late onset nephritis

	Early onset $N = 50$	Late onset $N = 21$	P
Glomerulonephritis classification			
Class II	5 (10%)	3 (14.2%)	0.79
Class III	10 (20%)	3 (14.2%)	
Class III+ V	2 (4%)	0	
Class IV	25 (50%)	13 (61.9%)	
Class IV+ V	1 (2%)	0	
Class V	7 (14%)	2 (9.5%)	
Induction treatment			
Cyclophosphamide	44 (88%)	20 (95.2%)	0.66
MMF	6 (12%)	1 (4.7%)	
Maintenance treatment			
Azathioprine	31 (62%)	14 (66.6%)	1.00
MMF	18 (36%)	7 (33. 3%)	
Treatment response in 2 years			
Total remission	30 (60%)	12 (57.1%)	0.35
Partial remission	10 (20%)	2 (9.5%)	
Treatment failure	10 (20%)	7 (33. 3%)	
Median creatinine (IQR)- mg/dL			
Initial	0.98 (0. 6-1. 3)	0.97 (0. 7-1. 3)	0.94
After 2 years	0.80 (0. 7-1.1)	0.74 (0. 6-1.0)	0.45
Creatinine clearence (mL/min)			
Initial (median;IQR)	83.5 (52. 3–120.6)	82. 3 (52. 7-89.0)	0.60
After 2 years (mean ± SD)	94.7 ± 38.7	97.0 ± 37.8	0.81
Positive anti-ds-DNA			
Initial	20 (40%)	13 (61.9%)	0.09
After 2 years	14 (28%)	9 (42.8%)	0.22
Median 24 h proteinuria (g/L) (IQR)			
Initial	2.9 (1. 7-5. 4)	2.0 (1. 2-5.1)	0.17
After 2 years	0.36 (0. 1-1.1)	0.35 (0. 1-1.0)	0.48
C3 (mg/dL)			
Initial (median; IQR)	72.5 (46. 5-99.6)	85.7 (56. 4–104.5)	0.22
After 2 years (mean ± SD)	109. 4±29. 4	103. 3±36. 3	0.45
Median C4 (IQR) (mg/dL)			
Initial	11.9 (7. 9-21.8)	12.0 (7.0–23.2)	0.93
After 2 years	19.0 (13. 9-26.9)	23.0 (13. 7-28.5)	0.68
Hemoglobine (g/dL)			
Initial (mean ± SD)	11.6 ± 2.2	12.8 ± 1.5	0.02
After 2 years (median;IQR)	13.0 (12.0–14.1)	12.6 (12.0–13.8)	0.58
SLEDAI			
Initial (mean ± SD)	14.8 ± 5. 4	13.2 ± 6.1	0.28
After 2 years (mean ± SD)	5.8± 4.6	6. 4± 4.8	0.59
Median SLICC/ACR DI (IQR)			
Initial	0 (0–1)	0 (0–1)	0.93
After 2 years	0 (0–2)	1.0 (0–2)	0.41
Interval (years) until first recurrence – median (IQR)	4.5 (2. 2-6.7)	3.0 (1.0–5.0)	0.07

N number, *IQR* interquartile range, *SD* standard deviation, *MMF* mophetyl mycophenolate, *SLEDAI* Systemic lupus erythematosus disease activity index, *SLICC/ACR DI* Systemic Lupus International Collaborating Clinics/ American College of Rheumatology Damage Index

have silent activity only disclosed by repeated biopsy [24]. However, repeated renal biopsy is an aggressive approach not well accepted by all patients. Nevertheless, this study highlights the fact that late and early nephritis have similar outcomes and should not be treated differently.

Conclusion

Our results have shown that nephritis onset is more common in the first 5 years after SLE diagnosis and that lupus patients with early and late onset nephritis share same clinical and serological characteristics. It also shows that these two situations had similar outcomes.

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Authors' contributions

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Competing interests

The authors declare that they have no competing interests.

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