ORIGINAL ARTICLE

Clinical characteristics of patients with Lupus Nephritis in a tertiary care hospital in Malaysia– A cross sectional study.

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Abstract

Introduction: Lupus nephritis (LN) is a common complication as evidenced clinically in 50-60% of patients with systemic lupus erythematosus (SLE) and is present histologically even in patients, without obvious symptoms of renal disease. Evaluating renal function in SLE patients is important because early detection with prompt treatment of renal involvement can significantly improve the prognosis.
Methods: The is a single-center cross-sectional study conducted in 2019 which included data regarding 235 LN patients from a tertiary nephrology clinic at Hospital Raja Permaisuri Bainun Ipoh, Perak, Malaysia. Basic clinical and demographic data for all LN patients were retrieved and analyzed from outpatient clinical records.
Results: A total of 235 LN patients with female to male ratio of 10:1. Ethnic stratification analysis showed that LN was highest in Malay ethnic group (49.4%, n=116) followed by Chinese (42.1%, n=99) and Indian (4.3%, n=10). The median age and duration of the disease were 41 (40 – 43) years and 5 (6 – 8) years respectively. Nephrotic presentation was significantly higher than nephritic presentation among all classifications of LN patients. Positive ANA and dsDNA with low C3 and C4 were frequently present in Class IV patients.
Conclusion: Proliferative lupus nephritis was the most common diagnosis amongst those who presented in our study cohort. The clinical and renal manifestations were relatively homogenous, although vary in frequency throughout different classes of LN. Multi-ethnicity with varies genetic background may contribute to the wide spectrum of LN phenotypes which need to be studied in future.

Keywords: Systemic lupus erythematosus, lupus nephritis, histology, clinical presentations.

Introduction

Lupus nephritis (LN) is a common manifestation and complication of more than 60% of systemic lupus erythematosus (SLE) cases which has significant negative impact on socio-economic burden attributed to high morbidity and mortality. [1, 2, 3, 4] Asian SLE patients shows higher incidence and prevalence of LN with more severe disease as compared to the Caucasians. [2, 5] Early detection of renal involvement with close monitoring of SLE patients is crucial to halt the progression of the disease, hence improves the overall outcome and survival. The objective of this study was to verify the clinic-pathological correlation of LN in nephrology division, Hospital Raja Permaisuri Bainun Ipoh, Malaysia.

Patients and methods

This was a cross-sectional study conducted at nephrology clinic Hospital Raja Permaisuri Bainun, Ipoh, Perak state of Malaysia in March 2019. Patients fulfilled American College of Rheumatology (ACR) Classification criteria for SLE, and Systemic Lupus International Collaborating Clinics (SLICC) were included in this study. [6, 7, 8] Patients' information were retrieved from clinic records i.e. the demographic variables, duration of disease, clinical manifestations and laboratory investigations including hematological and biochemistry profiles, and serology or immunology markers. Diagnosis of LN was confirmed by renal biopsy and as per the International Society of Nephrology/Renal Pathology Society 2003 Classification of Lupus Nephritis (ISN/RPS) criteria [9] as follows: Class I (minimal mesangial LN), Class II (mesangial proliferative LN), class III (focal LN), Class IV (diffuse LN), Class V (membranous LN), and Class VI (advanced sclerotic LN). The activity and chronicity index and score were based on the WHO and ISN/RPS classifications. Patient with histological evidence LN and fulfilled ≥ 4 ACR criteria for SLE is categorized as LN-positive. Patient diagnosed SLE or LN induced by drugs, overlapped syndrome, or mixed connective tissue disease were excluded. The clinical presentations were categorized as nephrotic, nephritic, acute glomerulonephritis (AGN) and rapidly progressive glomerulonephritis (RPGN). The glomerular filtration rate (GFR) was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) version 2009 equation. [10] The estimated glomerular filtration rate (eGFR) was categorized to 3 states using the Modification of Diet in Renal Disease equation [11] – state 1 (eGFR: > 60 ml/min); state 2 (eGFR: 30-60 ml/min); and state 3 (eGFR: <30 ml/min). The National Kidney foundation (NKF) classification of chronic kidney disease (CKD) was used to determine the staging of the CKD: Stage 0: no CKD; Stage 1: kidney damage with normal or increased eGFR (590ml/min/1.73m^2); Stage 2: kidney damage with mild decrease in eGFR (60-89ml/min/1.73m^2); Stage 3: moderate decrease in eGFR (30-59ml/min/1.73m2); Stage 4: severe decrease in eGFR (15-29ml/min/1.73m^2); Stage 5: kidney failure (<15ml/min/1.73m^2 or dialysis) [12].

Ethical approval

The study was approved by the institutional ethics committee (Universiti Kuala Lumpur Royal College of Medicine Perak and the Medical Research Ethics Committee (MREC) Ministry of Health Malaysia (NMRR: 19-79-45799).

Statistical analysis

Descriptive analysis of all demographic and clinical characteristics was performed using SPSS version 23 (institutional license). Means and standard deviations or median and interquartile ranges for numeric variables based on distribution of data, and frequencies for qualitative variables were measured. Non-parametric analyses were performed when dependent variables were either categorical or not-normally among different subcategories. *P* value of < 0.05 was considered as statistically significant.

Results

A total of 235 patients with LN were reviewed. LN was observed higher among females (90.6%) compared to males (9.4%) with approximate ratio of 10: 1. Malay ethnic group was dominant among LN patients (49.4%) followed by Chinese 42.1%) and Indian (4.3%). There was no significant difference between the 3 major ethnic groups with the LN classes. Nevertheless, LN III and IV were common in Malay (55.8%, 47.3%) and Chinese (34.9%, 41.8%) respectively. The peak incidence of LN occurred in between third and sixth decades of life with mean age of 41.4 years. The median age at presentation for female was 41.3 and 42.3 years for male but it was not significantly different across the LN classes. 83.8% of patients diagnosed LN more than 2 years duration. The median (IQR) duration of disease was 5 (2) years. Hypertension was manifested in 56.2% of patients and was commonly associated with LN III and IV. The median (IQR) serum creatinine at presentation was 67 (76 – 101) µmol/L and was significantly different across gender (P <0.0001) and based on hypertension status (P=0.021). The median (IQR) eGFR was 95(86.9 -95.3) mL/min/1.73 m^2 with CKD. There was no significant difference in GFR across LN classes. The highest mean GFR was found in LN II and V, though. Renal biopsies were performed on 195/235 (83.0%) patients with the following histological findings: I: 4 (1.7%), II: 12 (5.1%), III: 43 (18.3%), IV: 110 (46.8%) and V: 25 (10.6%). (P < 0.001). However, there was one missing report despite biopsy being performed. Histological evidence of LN from renal biopsy was significantly higher in female (90.8%, 177/195) than male (9.2%, 18/195) compared to without histological evidence or renal biopsy for both gender (P = 0.001).

ANA and anti-dsDNA antibody were positive in 65 (27.7%) and 64 (27.2%) respectively while low complement 3 and 4 were present in 49 (23.0%) and 38 (17.9%) of LN patients, respectively. There were no significant association between positive ANA in all LN classes at presentation. Of the 235 patients, 170 (72.3%) were ANA negative and there were no statistically significant differences in other SLE features according to ACR classification criteria between ANA-positive and negative LN patients. Nephrotic syndrome was the commonest presentation (146/214 - 68.2%) followed by nephritic (66/214 - 30.8%) and AGN. Class IV was the predominant histopathological finding identified in patients with nephrotic (72.7%) and nephritic (24.5%) presentations. The mode of clinical presentations was significantly different in different classes of LN (P <0.001). Significant proteinuria, more than 0.5 gm/24 hours was present in 54.9% of patients with 53.6% were having persistent proteinuria measured by urine dipstick. Nevertheless, proteinuria was substantially presence in all classes and more frequent in Class IV (68.2%, n=75/110) and nephrotic presentation (43.0%, n=101/235). The demographic characteristics, clinical manifestation and laboratory finding of patients with various classes of LN at time of presentation are shown in Table 1.

There was no significant difference in all classes of LN in relation to the CKD stages although higher proportion of CKD was noted among patients with LN class IV. A total of 58 out of 111 patients with CKD were with LN stage IV (Table 2).

Majority of LN patients were on corticosteroid therapy. Of the 160 (68.1%) patients who received hydroxychloroquine, 133 (56.6%) and 27 (11.5%) patients were with histological evidence, and without evidence or renal biopsy respectively. Azathioprine was used in 39.6% patients for induction or maintenance. Cyclophosphamide and mycophenolate mofetil were the most common induction agents in proliferative lupus nephritis (LN III and IV) (P= 0.004 and 0.02 respectively). None of the patients received biologic agents.

Discussion

LN prognosis has been progressively improved over the years with the advancement of treatment including immunosuppressant, biologics, dialysis, transplantation and better health care services and diagnostic facilities. However, in this region, the awareness among the community is still lacking due to multifactorial reasons such as multi-ethnicity with different genetic background.

The prognosis and survival of lupus nephritis patient has shown to be improving due to early detection and recognition, attributed to increase in awareness among patients. The collaboration between clinician, rheumatologist and nephrologist are deemed crucial in the management of LN as well. More than 80% of patients with histological evidence of LN was found from our series, although between 25 and 60% had been reported in the literature. [13, 14] This reflects the progress of improvement in the diagnostic and healthcare facilities, treatment and management including the optimum care for comorbid provided.

However, the unique multiethnic Malaysian population with different geographical and culture background, likewise other part of developing countries, still varies in their perception pertaining to unfamiliar, uncommon autoimmune diseases. The traditional beliefs especially in rural areas despite being advised medically, are yet to overcome. Hence, diagnosis of SLE is often delayed resulting in undesirable complications and contribute to high mortality and morbidity which significantly escalated among younger age group.

The prevalence of SLE in Malaysia has been reported 43/100,000 individuals.[15, 16] Chinese have the highest prevalence (57/100,000), followed by Malays (33/100,000) and Indians (14/100,000).[17, 18] Nevertheless, Jake WR *et al.* in their review had reveal that Asian countries have higher rates of lupus nephritis.[5]

The frequency of initial clinical presentation as per ACR classification criteria for SLE, show variability as compared to the large cohort study. [19]

In contrast to previous cohorts, the risk of LN in females exceed males in our study.[20, 21] The development of LN simultaneously present at the onset of SLE diagnosed in early 40's of age with gender equality in this study is consistent with Mak A *et al*. [22] but in contrast to younger age group in other studies. [14, 23] The lack of information to when the diagnosis of SLE before clinical nephritis developed or diagnosed presumably lead to this discordance. Culture belief, perception, and lack of awareness of the disease are additional possible factors that may delay the diagnosis of SLE in our community especially in rural areas. However, we did not include socio-behavioural aspect in this study. It has been shown that LN rarely developed after 5 years of SLE onset. [24]

Overall, across LN types, the cutaneous lupus of ACR domain in this study concurred with previous studies.[25, 26] The role of anti-dsDNA antibody in immunopathogenesis of LN has been widely studied and remained debatable.[27] Less than 30% of LN patients in the present study were ANA and anti-dsDNA positive with low C3 and C4. Nevertheless, the correlation between the positive serology and the LN activity could not be concluded due to insufficient data. Moreover, in our laboratory setting, qualitative anti-dsDNA Ab usually tested only when the ANA positive with homogenous pattern contributed to the discordance of the results.

Hypertension in this study was substantially higher than previous studies.[3, 28, 29, 30, 31] However, it is uncertain whether the hypertension diagnosed prior or at time of renal biopsy. There was no significant correlation between hypertension and WHO lupus nephritis classes which concurred the results from study by Mok *et*

al. [32] Similar findings reported in previous study by Naiker *et al*. [33] of which the prevalence was higher in severe proliferative LN.

Our study encountered several limitations among which were the lack of documentation of certain important data, and qualitative instead of quantitative laboratory results.

Conclusion

In conclusion, this is our first experience in analyzing the epidemiology of lupus nephritis in a single nephrology centre in Malaysia. Our study shows that clinical and renal manifestations were relatively homogenous, although vary in frequency throughout different classes of LN. Further study on the survival, outcome, treatment response and the risk predictors for development of LN in patients with SLE are needed.

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Declaration of Conflict of Interest

The authors declare that they have no known conflicting financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Table 1. Demographic, Clinical manifestations, Laboratory Parameters of Patients with WHO Lupus Nephritis classes at initial presentation.

	Without HPE evidence (without renal biopsy) n=41	WHO Lupus Nephritis Classification (with HPE evidence) Type I (n=4)	Type II (n=12)	Type III (n=43)	Type IV (n=110)	Type V (n=25)	*P*
Gender, n (%)							
Female	36 (87.8)	4 (100.0)	12 (100.0)	41(95.3)	98 (89.1)	22 (88.0)	NS
Male	5 (12.2)	0	0	2 (4.7)	12 (10.9)	3 (12.0)	
Age , median (IQR)*, years	42(23)	39(21)	41(17)	41(22)	41(21)	37(18)	NS
Ethnicity, n (%)							
Malay	18 (43.9)	3 (75)	5 (41.7)	24 (55.8)	52 (47.3)	14 (56.0)	NS
Chinese	23 (56.1)	1 (25)	5 (41.7)	15 (34.9)	46 (41.8)	9 (36.0)	
Indian	0	0	0	1 (2.3)	8 (7.3)	1 (4.0)	
Others	0	0	1 (8.3)	3 (7.0)	4 (3.6)	1 (4.0)	
Disease duration, median (IQR)*, years	5(7)	5(3)	3(14)	4(5)	5.5(5)	6(7)	NS
Co-morbid, n (%)							
- Hypertension	22 (53.7)	3 (75.0)	7(58.3)	28 (65.1)	74 (67.3)	14 (56.0)	NS
- Diabetes	0	1(25.0)	0	5 (11.6)	10 (9.1)	2 (8.0)	
- Hyperlipidemia	2 (4.9)	0	0	3(7.0)	3 (2.7)	0	
- Ischemic heart disease	0	0	0	0	3 (2.7)	0	
Proteinuria (>0.5 gm/24hours), n (%)	23 (56.1)	3 (75.0)	7 (58.3)	25 (58.1)	75 (68.2)	60(30.0)	NS
Serology: n (%)							
Positive ANA	11 (26.8)	0	6 (50.0)	22 (51.2)	40 (36.4)	9 (36.0)	†
Positive Anti-dsDNA	10 (24.4)	0	7 (58.3)	12 (27.9)	29 (23.6)	6 (24.0)	NS
Low C3	8 (19.5)	0	4 (33.3)	13 (30.2)	18 (16.4)	6 (24.0)	NS
Low C4	8 (19.5)	0	5 (41.7)	11 (25.6)	10 (9.1)	4 (16.0)	NS
Positive Anti-Sm	0	0	0	0	2 (1.8)	0	NS
Clinical presentation: n (%)							
Nephrotic	17 (41.5)	3 (75.0)	7 (58.3)	25 (58.1)	80 (72.7)	14 (56.0)	0.001
Nephritic	7 (17.1)	1 (25.0)	4 (33.3)	17 (39.5)	27 (24.5)	10 (40.0)	
AGN	0	0	0	0	2 (1.8)	0	
Other SLE features: n (%)							
Malar	3 (7.3)	0	5 (41.7)	13 (30.2)	30 (27.3)	6 (24.0)	0.010
Discoid	1 (2.4)	0	0	3 (7.0)	11 (10.0)	3 (12.0)	NS
Photosensitive rashes	3 (7.3)	3 (75.0)	0	6 (13.9)	9 (8.2)	2 (8.0)	NS
Mucosal Ulcer	3 (7.3)	0	2 (16.7)	6 (13.9)	9 (8.2)	3 (12.0)	NS
Vasculitis	1 (2.4)	0	1 (8.3)	6 (13.9)	11 (10.0)	2 (8.0)	NS
Alopecia	6 (14.6)	0	1 (8.3)	13 (30.2)	32 (29.1)	9 (36.0)	NS
Arthritis	15 (36.6)	2 (50.0)	4 (33.3)	14 (32.6)	41 (37.3)	9 (36.0)	NS
Myositis	0	0	1 (8.3)	1 (2.3)	4 (3.6)	1 (4.0)	NS
Pericarditis	1 (2.4)	1 (25.0)	0	2 (4.6)	2 (1.8)	0	NS
Serum creatinine, (umol/L) Median (IQR)*	77.0(40.5)	69.3(45.7)	57.5(28.5)	61.0(35.0)	73.0(34.0)	60(30.0)	NS
GFR, (ml/min), Median (IQR)*	91.1(55.5)	97.5(53.5)	108.0(39)	102.0(44.0)	91.5(38.7)	113.0(40.5)	NS
Treatment: n (%)							
Hydroxychloroquine	27 (65.8)	3 (75.0)	8 (66.7)	36 (83.7)	64 (58.2)	22 (88.0)	0.012
Methotrexate	0	0	0	0	3 (2.7)	1 (4.0)	NS
Azathioprine	18 (43.9)	1 (25.0)	6 (50.0)	27 (62.8)	46 (41.8)	13(52.0)	NS
Cyclosporine A	1 (2.4)	0	0	0	8 (7.3)	2 (8.0)	NS
Cyclophosphamide	8 (19.5)	0	4 (33.3)	13 (30.2)	55 (50.0)	7 (28.0)	0.004
Mycophenolate	9 (21.9)	0	2 (16.7)	12 (27.9)	50 (45.5)	8 (32.0)	0.020
Prednisolone	33 (80.5)	4 (100.0)	12 (100.0)	42 (97.7))	100 (90.9)	22 (88.0)	NS
Methylprednisolone IV	3 (7.3)	0	1 (8.3)	3 (7.0)	8 (7.3)	3 (12.0)	NS
NSAID	1 (2.4)	0	1 (8.3)	3 (7.0)	3 (2.7)	2 (8.0)	NS

*Data are not normally distributed, †Invalid data due to insufficient information.
Abbreviation: LN, lupus nephritis; ANA, anti-nuclear antibody; dsDNA, double-stranded DNA; C, complement; GFR, glomerular filtration rate; AGN, acute glomerulonephritis; RPGN, rapidly progressive glomerulonephritis; NSAID, Non-Steroidal anti-inflammatory drug; IV, intravenous; NS, not significant; WHO, World Health Organization; IQR, interquartile range.

Table 2. CKD stages in various WHO LN classes.

CKD stages (eGFR ml/min/1.73m^2)	LN I (n=4)	LN II (n=12)	LN III (n=43)	LN IV (n=110)	LN V (n=25)	*P*
1 (≥90)	2 (50.0)	9 (75.0)	25 (58.1)	58 (57.2)	17 (68.0)	NS
2 (60-89)	1 (25.0)	1 (8.3)	11 (25.6)	23 (20.9)	4 (16.0)	
3 (30-59)	0	1 (8.3)	4 (9.3)	14 (12.7)	2 (8.0)	
4 (15-29)	0	0	0	4 (3.6)	1 (4.0)	
5 ((<15)	0	0	0	2 (1.8)	0	

Abbreviation: LN: lupus nephritis, NKF classification of CKD: Stage 0: no CKD; Stage 1: kidney damage with normal or increased eGFR; Stage 2: kidney damage with mild decrease in eGFR; Stage 3: moderate decrease in eGFR; Stage 4: severe decrease in eGFR; Stage 5: kidney failure; NS, not significant

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