

Clinical Predictors of Nephritis in Systemic Lupus Erythematosus

J Thumboo,**MBBS, M Med (Int Med), MRCP (UK)*, K Y Fong,***FAMS, MBBS, M Med (Int Med)*, H P Chia,****MBBS, M Med (Occup Med)*,
H H Chng,*****FAMS, MBBS, M Med (Int Med)*, E T Koh,***FAMS, MBBS, MRCP (UK)*, K H Leong,†*FAMS, MBBS, FRCP (Edin)*,
W H Koh,***FAMS, MBBS, MRCP (UK)*, H S Howe,***FAMS, MBBS, M Med (Int Med)*, K P Leong,**MBBS, MRCP (UK)*,
M L Boey,‡*FAMS, M Med (Int Med), MD*, P H Feng,§*FAMS, FRCP (Edin), MD*

Abstract

We identified clinical predictors of lupus nephritis presenting more than 6 months after the diagnosis of lupus in a cohort of 335 lupus patients. Almost 24% (80/335) of patients developed nephritis more than 6 months after the diagnosis of lupus. Using a Coxproportional hazards model, we found hypertension, thrombocytopaenia and leukopaenia to be associated with lupus nephritis presenting more than 6 months after diagnosis, with adjusted relative risks of 2.5 (95% CI 1.3 to 4.7), 4.3 (95% CI 1.7 to 10.8) and 3.2 (95% CI 1.7 to 6.2) respectively. In this cohort, hypertension, thrombocytopaenia and leukopaenia were associated with lupus nephritis presenting more than 6 months after the diagnosis of lupus.

Ann Acad Med Singapore 1998; 27:16-20

Key words: Asia, Hypertension, Leukopaenia, Risk factors, Thrombocytopaenia

Introduction

Lupus nephritis is a common manifestation of lupus associated with significant morbidity and mortality.¹ The use of cytotoxic agents has resulted in improved renal outcomes² but is associated with considerable morbidity, and their role in the management of lupus nephritis is not universally accepted.³ A complementary strategy might be to reduce the incidence of lupus nephritis in patients with lupus. We hypothesised that some clinical features of lupus patients might predict the later development of nephritis. Identification of such parameters might give insight into the pathogenesis of lupus nephritis and offer avenues for therapeutic intervention. We used data from an existing database of lupus patients to study this hypothesis.

Materials and Methods

Patient Population and Definitions

A retrospective cohort study was conducted using an existing database of patients with lupus on follow up at

the Department of Rheumatology and Immunology, Tan Tock Seng Hospital, the sole Rheumatology unit in Singapore. Data on this cohort of patients were abstracted from medical records by physician abstractors. Patients with lupus were reviewed regularly, the frequency of review being dictated by disease severity and activity. Patient data were abstracted using a standardised, pre-tested protocol. Lupus was defined as the presence of 4 or more of the 1982 revised American Rheumatism Association (ARA) criteria,⁴ and the date of diagnosis as the date when 4 or more ARA criteria were first noted by a physician. The date of first manifestation of selected clinical features was recorded. The date of onset of lupus nephritis was taken as the date of first manifestation of persistent proteinuria (>0.5 g/day or >3+ on dipstick if quantitation was not performed) or cellular casts as defined in the 1982 ARA criteria. Patients with lupus nephritis present at diagnosis or presenting within 6 months of diagnosis were excluded from this analysis on the assumption that factors predis-

* Registrar

** Consultant

**** Senior Consultant

† Visiting Consultant

‡ Senior Consultant and Head of Department

§ Senior Consultant and Professor of Medicine

Department of Rheumatology and Immunology

Tan Tock Seng Hospital

*** Lecturer

Department of Community, Occupational and Family Medicine

National University of Singapore

Address for Reprints: Dr Julian Thumboo, Department of Rheumatology and Immunology, Tan Tock Seng Hospital, Moulmein Road, Singapore 308433.

posing to the development of nephritis in this period would not be easily amenable to therapeutic intervention. Hypertension was defined as a blood pressure of greater than 160/90 mm Hg on three separate occasions.⁵ Diabetes mellitus was defined as either the presence of polyuria and polydipsia and a random blood glucose level of more than 11 mmol/L or fasting blood glucose level of more than 7 mmol/L, or two blood glucose values greater than those previously stated in the absence of symptoms.⁶ Explanatory variables entered in the Cox proportional hazards model were defined as follows: duration of symptoms (defined as the duration in years from onset of the first ARA criteria to diagnosis); ethnicity (Chinese, Malay or Indian); age at diagnosis in years; gender; presence or absence of thrombocytopaenia ($<100\,000/\text{mm}^3$), leukopaenia ($<4000/\text{mm}^3$ in the absence of viral infection or drugs known to cause leukopaenia) and hypertension or diabetes mellitus prior to the development of lupus nephritis. Case records of 624 patients were reviewed during the period from November 1995 to July 1996. Fifty-seven patients were excluded from the study because they had less than 4 ARA criteria documented, 40 were excluded because they had diagnosis of lupus at less than 16 years of age, 51 were excluded because they were residing outside of Singapore, 4 because they belonged to ethnic groups other than those being studied and 137 because lupus nephritis developed less than 6 months after diag-

nosis. Patients residing outside Singapore were excluded from analysis to minimise any influence of differing environmental risk factors. Patients less than 16 years of age at diagnosis were excluded because disease manifestations in this group differ from those in adults.⁷

Statistical Analysis

Data were entered into a Microsoft Access 7.0 database and imported into the Statistical Package for the Social Sciences (SPSS) 6.0 for Windows programme for analysis. Differences in means were assessed using the unpaired 2 tailed t-test, and differences in proportions using the chi-square test. A Cox proportional hazards model was used to identify explanatory variables associated with lupus nephritis presenting more than 6 months after the date of diagnosis (the outcome variable). The date of diagnosis of lupus was taken as the start time for analysis. Unadjusted and adjusted relative risks with 95% confidence intervals (95% CI) were calculated for each variable. A *P* value of less than 0.05 was considered statistically significant.

Results

Three hundred and thirty-five patients had no features of lupus nephritis 6 months after diagnosis of lupus and formed the study cohort. The demographic features of this cohort are summarised in Table I. Lupus

TABLE I: PREVALENCE OF DEMOGRAPHIC AND SELECTED CLINICAL FEATURES OF THE STUDY COHORT

	Renal involvement		<i>P</i> value
	Yes (n = 80)	No (n = 255)	
Chinese:Malay:Indian	68:9:3	208:32:15	0.10
Male:Female (Ratio)	7:73 (1:10.4)	15:240 (1:16)	0.52
Mean age ($\pm$ SD) at diagnosis of lupus (years)	29.8 ($\pm$ 8.6)	33.0 ($\pm$ 11.6)	0.03
Mean duration ($\pm$ SD) of symptoms before diagnosis (years)	0.1 ($\pm$ 3.1)	1.2 ($\pm$ 3.3)	0.02
Number (%) with thrombocytopaenia			
Prior to the onset of nephritis	12 (15)	NA	
Cumulative	20 (25)	65 (25.5)	
Number (%) with cutaneous vasculitis			
Prior to the onset of nephritis	18 (22.5)	NA	
Cumulative	24 (30.0)	60 (23.5)	
Number (%) with leukopaenia			
Prior to the onset of nephritis	25 (31.3)	NA	
Cumulative	35 (43.8)	115 (45.1)	
Number (%) with diabetes mellitus			
Prior to the onset of nephritis	1 (1.3)	NA	
Cumulative	7 (8.8)	16 (6.3)	
Number (%) with hypertension			
Prior to the onset of nephritis	18 (22.5)	NA	
Cumulative	43 (53.8)	55 (21.6)	

SD: standard deviation; NA: not applicable

nephritis subsequently developed in 23.9% (80/335) of these patients, a mean of 4.78 years (range 0.56 to 18.25 years) after diagnosis. Patients who developed lupus nephritis were significantly younger at diagnosis and had a shorter duration of symptoms before diagnosis than those patients who did not develop nephritis. Of the 80 patients who developed nephritis, persistent proteinuria developed in 94.4% (17/18) of patients with nephritis preceded by hypertension and 93.5% (58/62) with nephritis not preceded by hypertension. Cellular casts developed in 44.4% (8/18) of patients with nephritis preceded by hypertension and 53.2% (33/62) of patients with nephritis not preceded by hypertension. The mean duration of hypertension prior to the onset of nephritis was 4.2 years (range 0.1 to 14.3 years), that of thrombocytopenia and leukopenia being 4.4 years (range 0.7 to 16.9 years) and 3.8 years (range 0.4 to 16.5 years), respectively.

Explanatory variables entered in the Cox proportional hazards model are listed in Table I. On univariate analysis, cutaneous vasculitis, thrombocytopenia, leukopenia and hypertension were associated with the development of nephritis (Table II). After adjusting for the influence of other explanatory variables using multivariate analysis, only hypertension, thrombocytopenia or leukopenia present before the onset of renal involvement were associated with lupus nephritis occurring more than six months after diagnosis, with adjusted relative risks of 2.5 (95% CI 1.3 to 4.7), 4.3 (95% CI 1.7 to 10.8) and 3.2 (95% CI 1.7 to 6.2), respectively.

TABLE II: COX PROPORTIONAL HAZARDS MODEL OF CLINICAL FEATURES ASSOCIATED WITH NEPHRITIS PRESENTING MORE THAN 6 MONTHS AFTER THE DIAGNOSIS OF LUPUS

Variable	Unadjusted		Adjusted	
	Relative Risk	95% CI	Relative Risk	95% CI
Malay ethnicity*	0.8	0.4 to 1.5	0.2	0.0 to 0.6
Indian ethnicity*	0.8	0.2 to 2.5	1.0	0.0 to 3.3
Male gender	0.7	0.3 to 1.5	0.6	0.3 to 1.4
Duration of symptoms before diagnosis (per year)	0.9	0.8 to 1.0	0.9	0.8 to 1.0
Age at diagnosis (per year)	1.0	0.97 to 1.01	1.0	0.97 to 1.02
Thrombocytopenia [†]	6.4	3.5 to 12.0	4.3	1.7 to 10.8
Cutaneous vasculitis [†]	4.2	2.5 to 7.1	1.7	0.8 to 3.5
Leukopenia [†]	5.2	3.2 to 8.7	3.2	1.7 to 6.2
Diabetes mellitus [†]	3.5	0.5 to 25.5	4.7	0.6 to 34.7
Hypertension+	4.7	2.7 to 7.9	2.5	1.3 to 4.7

* As compared with Chinese ethnicity

[†] Present prior to the onset of nephritis

95% CI: 95% confidence interval

Discussion

Of the clinical features assessed in this study, hypertension, thrombocytopenia or leukopenia present before the onset of renal involvement were associated with lupus nephritis presenting more than six months after diagnosis. These associations persisted after statistical adjustment for differences in age at diagnosis and mean duration of symptoms between patients with and without nephritis. Our findings are consistent with those of Petri et al,⁸ who identified hypertension as a risk factor for the development of important renal disease. There are several mechanisms through which hypertension may be associated with the subsequent development of lupus nephritis. Endothelial cell dysregulation occurs in lupus⁹ and in hypertension,¹⁰ with hypertension predisposing to the development of immune-mediated glomerulonephritis in genetically susceptible rats.¹¹ A genetic predisposition to both hypertension and nephritis in lupus patients could also account for our findings, as is seen in patients with primary glomerulonephritis¹² and type I diabetes mellitus.¹³ Hypertension may also be a marker for clinically inapparent lupus nephritis¹⁴ which may subsequently manifest clinically. Essential hypertension itself may be associated with proteinuria,¹⁵ but albuminuria >50 µg/ml occurred in only 3% of hypertensive non-diabetic hypertensive subjects less than 60 years of age¹⁶ and was therefore not a major consideration in this study, as none of the subjects with nephritis were over 60 years of age at onset of nephritis. Corticosteroids cause a rise in blood pressure in 10% to 19% of lupus patients¹⁷ and are more likely to be given to patients with more severe manifestations of lupus, possibly resulting in a false association between hypertension and the development of lupus nephritis.

The finding that thrombocytopenia and leukopenia were predictive of subsequent renal involvement was unexpected. On univariate analysis, cutaneous vasculitis, leukopenia, thrombocytopenia were associated with the development of lupus nephritis, but only thrombocytopenia and leukopenia retained significance as risk factors on multivariate analysis. This suggests that a common mechanism—possibly active disease resulting in immune-mediated cytopenias¹⁸—rather than cytopenias per se may account for the observed association. Thrombocytopenia has been associated with increased mortality in several cohorts of lupus patients.¹⁸ This may be mediated in part through the association of thrombocytopenia with lupus nephritis shown in our study.

Treatment of hypertension in lupus patients without nephritis may reduce the risk of developing lupus nephritis. Reversal of endothelial cell dysfunction with anti-hypertensive therapy has been noted in animal models of hypertension.¹⁹ Aggressive control of hypertension also slows the decline in glomerular filtration

rate seen in patients with chronic renal disease.²⁰ Leukopaenia per se is not an indication for escalation of immunosuppressive therapy unless severe, but if persistent should prompt a search for other evidence of active lupus.

Although hypertension, thrombocytopaenia and leukopaenia predicted the later development of nephritis, these also occurred in a large number of patients who did not subsequently develop nephritis. This suggests that other factors may contribute to the development of nephritis. Factors associated with the development of lupus nephritis include genetic²¹ or ethnic background,²² younger age at onset of lupus,²³ autoantibody profiles,²⁴⁻²⁶ circulating immune complexes to ds-DNA,^{27,28} corticosteroid therapy⁸ and patient compliance.⁸ Environmental triggers, disease severity and activity, other immune complex mediated manifestations of lupus (e.g. vasculitis, thrombocytopaenia or leukopaenia) and immunosuppressive therapy may also contribute to the development of lupus nephritis. We studied the influence of some of these factors but the retrospective nature of this study did not allow us to assess the effect of genetic or environmental factors, disease flares, serial complement and autoantibody levels or compliance on the development of lupus nephritis. Apart from corticosteroid therapy, these other factors are unlikely to cause an increase in blood pressure but may be independently associated with the development of lupus nephritis.

This study has several limitations. As information on genetic and environmental factors, autoantibody and complement profiles, patterns of immunosuppressive and corticosteroid usage and patient compliance were not available for some patients, these variables were not included in the Cox model. We were therefore unable to assess the association of these variables with the development of nephritis, nor could we determine their effect on the association of hypertension, thrombocytopaenia or leukopaenia and the subsequent development of nephritis. We also could not adjust for potential confounding effects of corticosteroid therapy on blood pressure.

In summary, in this cohort of lupus patients, hypertension, thrombocytopaenia and leukopaenia were associated with lupus nephritis presenting more than 6 months after the diagnosis of lupus. These associations need to be confirmed in other studies. Elucidation of possible mechanisms underlying this association may provide insights into the pathophysiology of lupus and may suggest strategies for the primary prevention of lupus nephritis.

Acknowledgements

We would like to thank Drs Chew Sze Mun, Chai Ping, Goh Lay Hoon, Goon Teik Jin, Lau Tang Ching, Lim Wei

Shen, Pek Wee Yang, Tong Khim Leng, Yang Wei Lyn, Research Nurse M H Wong, Mr Phun Chin Jin and the staff of the Medical Record Office, Tan Tock Seng Hospital, for their assistance.

REFERENCES

- Wallace DJ. Prognostic subsets and mortality in systemic lupus erythematosus. In: Wallace DJ, Hahn B H, editors. *Dubouis Lupus Erythematosus*. Philadelphia: Lea and Febiger, 1994:606-15.
- Balow J E, Boumpas D T, Fessler B J, Austin III H A. Management of lupus nephritis. *Kidney Int* 1996; 49(Suppl 53):588-92.
- Donadio J V, Glassock R J. Immunosuppressive therapy in lupus nephritis. *Am J Kidney Dis* 1993; 21:239-50.
- Tan E M, Cohen A S, Fries J F, Masi A T, McShane D J, Rothfield N F, et al. The 1982 revised criteria for the classification of systemic lupus erythematosus. *Arthritis Rheum* 1982; 25:1271-7.
- Williams G H. Hypertensive vascular disease. In: Wilson J E, Braunwald E, Isselbacher K J, Petersdorf R G, Martin J B, Fauci A S, et al, editors. *Harrison's Principles of Internal Medicine*. New York: McGraw-Hill, 1991:1001-15.
- Alberti K G M M, Hockday T D R. Diabetes Mellitus. In: Weatherall D J, Ledingham J G G, Warrell D A, editors. *Oxford Textbook of Medicine*. London: Oxford Univ Press, 1983:9.5-9.49.
- Tucker L B, Menon S, Isenberg D A. Systemic lupus in children: daughter of the Hydra? *Lupus* 1995; 4:83-5.
- Petri M, Perez-Gutthann S, Longenecker J C, Hochberg M. Morbidity of systemic lupus erythematosus: role of race and socio-economic status. *Am J Med* 1991; 91:345-53.
- Belmont H M, Abramsom S B, Lie J T. Pathology and pathogenesis of vascular injury in systemic lupus erythematosus. *Arthritis Rheum* 1996; 39:9-22.
- Tolins J I, Schultz P, Raij L. Mechanisms of hypertensive glomerular injury. *Am J Cardiol* 1988; 62:54G-58G.
- Raij L, Azar S, Keane W. Mesangial immune injury, hypertension and progressive glomerular damage in Dahl rats. *Kidney Int* 1984; 26:137-43.
- Schmid M, Meyer S, Wegner R, Ritz E. Increased risk of hypertension in glomerulonephritis. *J Hypertens* 1990; 8:573-7.
- Krolewski A S, Canessa M, Warram J H, Laffel L M, Christlieb A R, Knowler WC, et al. Predisposition to hypertension and susceptibility to renal disease in insulin-dependant diabetes mellitus. *N Engl J Med* 1988; 318:140-5.
- Font J, Torras A, Cervera R, Darnell A, Rervert L, Ingelmo M. Silent renal disease in systemic lupus erythematosus. *Clin Nephrol* 1987; 27:283-8.
- Rambausek M, Fliser D, Ritz E. Albuminuria of hypertensive patients. *Clin Nephrol* 1992; 38(Suppl 1):S40-5.
- Ritz E, Nowicki M, Fliser D, Horner D, Klimm H-P. Proteinuria and hypertension. *Kidney Int* 1994; 46(Suppl 47):S76-S80.
- Quismono F P. Cardiac abnormalities in systemic lupus erythematosus. In: Wallace DJ, Hahn B H, editors. *Dubouis Lupus Erythematosus*. Philadelphia: Lea and Febiger, 1994:606-15.
- Lawrence J, Wong J E L, Nachman R. The cellular haematology of systemic lupus erythematosus. In: Lahita R G, editor. *Systemic Lupus Erythematosus*. New York: Churchill Livingstone, 1992:782.
- Luscher T F. The endothelium in hypertension: bystander, target or mediator? *J Hypertens* 1994; 12(Suppl 10):S105-S116.
- Peterson J C, Adler S, Burkart J M, Greene T, Hebert L A, Hunsicker L G, et al. Blood pressure control, proteinuria and the progression of renal disease. *Ann Intern Med* 1995; 123:754-62.
- Freedman B I, Spray B J, Heise E R, Espeland M A, Canzanella V J. A race-controlled human leucocyte antigen frequency analysis in lupus nephritis. *Am J Kidney Dis* 1993; 21:378-82.

22. Studenski S, Allen N B, Caldwell D S, Raice J R, Polisson R P. Survival in systemic lupus erythematosus. *Arthritis Rheum* 1987; 30:1326-32.
 23. Koh E T, Boey M L. Late onset lupus: A clinical and immunological study in a predominantly Chinese population. *J Rheumatol* 1994; 21:1463-7.
 24. Harlrey J B, Gaither K K. Autoantibodies. *Rheum Dis Clin North Am* 1988; 14:43-56.
 25. Homma M, Mimori T, Takeda Y, Akama H, Yoshida T, Ogasawara T, et al. Autoantibodies to the Sm antigen: Immunological approach to clinical aspects of systemic lupus erythematosus. *J Rheumatol* 1987; 14(Suppl 13):188-93.
 26. Maddison P J, Isenberg D A, Goulding N J, Leddy J, Skinner R P. Anti La (SSB) identifies a distinctive subgroup of systemic lupus erythematosus. *Br J Rheumatol* 1988; 27:27-31.
 27. Sasaki T, Muryoi T, Hatakeyama A, Suzuki M, Sato H, Seino J, et al. Circulating anti-DNA immune complexes in active lupus nephritis. *Am J Med* 1991; 91:355-62.
 28. Hochberg M C, Boyd R E, Ahearn J M, Arnett F C, Bias W B, Provost T T, et al. Systemic lupus erythematosus: a review of clinico-laboratory features and immunologic markers in 150 patients with emphasis on demographic subsets. *Medicine* 1985; 64:285-95.
-