Systemic lupus erythematosus. III. Observations on clinical renal involvement and follow up of renal function: Dutch experience with 110 patients studied prospectively

J C NOSSENT,¹ WILLEM BRONSVELD,² AND A J G SWAAK¹

From the ¹Department of Rheumatology, Daniel den Hoed Clinic, Rotterdam, The Netherlands; and the ²Department of Internal Medicine, Medical Center, Alkmaar, The Netherlands

SUMMARY A prospective study of 110 patients with systemic lupus erythematosus (SLE) was undertaken to evaluate the reliability of clinical signs of lupus nephritis, which developed in 39 (35%) patients. Those patients with SLE who showed no clinical signs of lupus nephritis had an excellent survival rate (10 year survival 93%) and retained normal renal function (serum creatinine <130 µmol/l); clinical lupus nephritis developed mainly in the first three years after diagnosis of SLE and was associated with a decreased survival rate (10 year survival 62%). Increased mortality was found in male patients with lupus nephritis over 25 years of age and in female patients with lupus nephritis under 25 years of age, while renal failure rates did not differ between these groups. Treatment of lupus nephritis with high dose prednisone alone or in combination with immunosuppressants did not result in differences in patient survival or renal function preservation. It was concluded that clinical variables are a reliable guide in the management of patients with SLE, and routine use of renal biopsy in these patients is rejected.

Nearly all patients with systemic lupus erythematosus (SLE) have histological abnormalities in renal biopsy specimens,^{1–3} and sometimes severe proliferative lesions are present without clinical renal abnormalities.^{4–5} As the occurrence of renal disease is the most important prognostic factor in patients with SLE^{6–7} the routine use of renal biopsy in all such patients to record glomerular disease and guide treatment has been advocated,^{4–5} but the issue is highly controversial.^{8–9}

We followed up 110 patients with SLE to study the disease course of those patients judged to have renal involvement on the basis of clinical variables, and compared them with patients without clinical signs of renal involvement.

Patients and methods

Patients fulfilling four or more American Rheumatism Association (ARA) criteria for SLE¹⁰ were

included in the study and followed up by one of the authors at our lupus outpatient clinics. The clinics started in 1972 and the end point for this study was 1 January 1987. Uniformity in follow up was ensured by standardised clinical record forms, while regular sessions on patient management ensured uniformity of therapeutic measurements. The preliminary ARA criteria¹¹ were used throughout the study; use of the revised ARA criteria¹⁰ did not result in significant differences in our study population.

Clinical manifestations of lupus nephritis were defined as one or more of the following: proteinuria >0.5 g/24 h, persistent urinary sediment abnormalities showing cellular casts, or a decrease of glomerular filtration rate (measured by creatinine clearance) of more than 20 ml/min within a period of three months; only those manifestations that could be shown on two separate occasions and for which no other explanation (infection, hypertension, diabetes mellitus) was available were considered as evidence for lupus nephritis. In 30 of the 39 patients (77%) suspected of lupus nephritis a renal biopsy was performed, with the following distribution according to WHO classification: class I: 1, class II: 2, class III:

Accepted for publication 15 February 1989.

Correspondence to Dr J C Nossent, Department of Rheumatology, Daniel den Hoed Clinic, PO Box 5201, 3008 AE Rotterdam, The Netherlands.

3, class IV: 16, class V: 4, and mixed group: 4. Nine patients had no histological confirmation of lupus nephritis owing to insufficient biopsy material or patient refusal.

TREATMENT OF LUPUS NEPHRITIS

Treatment of lupus nephritis consisted either of high dose prednisone (1.5 mg/kg) once daily alone (n=16), or in combination with azathioprine (1.5–2.5 mg/kg; n=19) or cyclophosphamide (1–3 mg/kg; n=4). After six weeks prednisone was gradually tapered, while immunosuppressants were continued for at least six months.

HYPERTENSION

Hypertension was considered present when diastolic pressure exceeded 90 mmHg on two different observations and was treated in a stepped-care way with diuretics, β blockers, and vasodilators respectively.

STATISTICS

Statistical evaluation was by Student's *t* test for group differences of mean values, the χ^2 test for absolute numbers, the two tailed Mann-Whitney U test for non-parametric data, and with computerised Kaplan-Meier analysis of survival curves (STATA). In the calculation of the survival curves for patients with SLE without lupus nephritis death was used as end point, while for curves of patients with SLE and lupus nephritis 'death and terminal renal insufficiency ('renal death') were taken as end point. Statistical significance was defined as *p* values <0.05. Unless stated otherwise, values are expressed as mean (SEM).

Results

PATIENT CHARACTERISTICS

Of 110 patients with SLE, 39 (35%) developed clinical lupus nephritis during our study (Table 1).

Table 1 Demographic data on 110 patients with systemic lupus erythematosus (SLE) with or without clinical renal involvement

	Nephritis (n=39)	No nephritis (n=71)
Number (%) of patients	39 (35)	71 (65)
Age at diagnosis of SLE (years)‡	33.1 (2.5)	40.3 (1.8)*
Follow up (months)‡	87.7 (8.6)	108.6 (7.2)
Patients receiving dialysis (n)	8	0†

**p*<0.05.

†*p*<0.001.

‡Values are mean (SEM).

Table 2 Mortality in patients with systemic lupus erythematosus (SLE) with or without lupus nephritis

	Nephritis (n=39)	No nephritis (n=71)
Non-survivors (%)	10 (26)	4 (6)*
Number of male deaths (% of male patients)	5 (56)	0 (0)†
Age ≤25	0 (0)	0 (0)
Age >25	5 (56)	0 (0)†
Number of female deaths (% of female patients)	5 (17)	4 (6)
Age ≤25	4 (13)	1 (2)‡
Age >25	1 (3)	3 (5)
Time between diagnosis of SLE and death (months)§	67.8 (14.8)	168.5 (44.2)

**p*<0.01.

†*p*<0.001.

‡*p*<0.05.

§Values are mean (SEM).

No significant differences were found with respect to sex distribution in either group. Mean age at diagnosis of SLE was significantly lower for patients with lupus nephritis, however, than for those without (33.1 v 40.3 years). Mean follow up for *all* patients was 89.9 months with no significant differences between groups. The need for renal replacement treatment did not arise in the group without lupus nephritis, whereas eight patients with lupus nephritis needed dialysis (21% of all patients with lupus nephritis). Early treatment with steroids (within two years after SLE was established) was started in 45% of patients, who later developed clinical signs of lupus nephritis (n=20) and in 43.6% of patients who never developed clinical lupus nephritis (*p*>0.05).

MORTALITY

The overall mortality of patients with lupus nephritis was significantly greater than for those without 26% v 6%; *p*<0.01) (Table 2). This difference was much more pronounced in male than in female patients: male patients with lupus nephritis had a 56% mortality compared with 0% in men without nephritis (*p*<0.001), whereas female patients with SLE with or without lupus nephritis showed no significant difference in mortality (17% v 6%). Further analysis showed that non-surviving male patients with lupus nephritis were all above 25 years of age at the time of diagnosis, whereas non-surviving female patients with lupus nephritis were mostly younger than 25 years of age. The period between the diagnosis of SLE and the moment of death was significantly

longer in patients without lupus nephritis than in those with the disease (168.5 months v 67.8 months). Table 3 lists the causes of death. Four of the eight patients receiving dialysis died owing to infections or cardiovascular causes. When the patients with lupus nephritis were analysed as a separate group (Table 4) no difference between fatal and non-fatal lupus nephritis was observed for the period between diagnosis of SLE and manifestation of lupus nephritis, or serum creatinine concentration at the moment lupus nephritis was diagnosed; mortality was greater for female patients with lupus nephritis under 25 years at the time of diagnosis of lupus nephritis, however.

RENAL FAILURE

Dialysis was necessary in eight patients with lupus nephritis; when compared with patients with lupus nephritis maintaining life supporting renal function no differences could be found in sex, age, initial serum creatinine values, and treatment (Table 5).

IMPACT OF LUPUS NEPHRITIS ON SURVIVAL FOR PATIENTS WITH SLE

Actuarial survival curves for patients with SLE with or without lupus nephritis (Fig. 1) were significantly different ($p < 0.001$), showing lupus nephritis to be a major factor in decreased survival of patients with SLE.

Table 3 Cause of death of 14 patients with systemic lupus erythematosus (SLE), subdivided according to the presence or absence of lupus nephritis

Sex/age	SLE related	Non-SLE related	Postmortem examination
<i>With nephritis (n=10)</i>			
F, 24	Recent pleuropericarditis	—	—
M, 58	Renal failure	Sepsis while receiving dialysis	+
F, 22	Renal failure	Peritonitis while receiving CAPD*	—
M, 57	Cerebral involvement	Suicide	—
F, 20	—	Bacterial encephalitis	+
F, 80	Renal insufficiency	Cardiac insufficiency/pneumonia	+
F, 33	Haemorrhagic pneumonitis	—	+
M, 67	Renal failure	Cardiac insufficiency	+
M, 46	Renal failure	Septic shock	+
M, 68	Renal insufficiency	Ruptured cardiac aneurysm	+
<i>No nephritis (n=4)</i>			
F, 77	—	Bronchopneumonia	—
F, 64	—	Myocardial infarction	+
F, 42	—	Gram negative sepsis	+
F, 33	Intracerebral bleeding with thrombocytopenia	—	+

*CAPD=continuous ambulatory peritoneal dialysis.

Table 4 Differences between surviving and non-surviving patients with lupus nephritis

	Died (n=10)	Alive (n=29)
Period between diagnosis of SLE and manifestation of lupus nephritis (months)†	36.1 (12.0)	16.7 (4.7)
Observation period (months)†	67.8 (14.8)	82.6 (10.0)
Median serum creatinine at diagnosis of lupus nephritis ($\mu\text{mol/l}$)	113.5	88.0
Male patients		
Age ≤ 25 , serum creatinine $< 130 \mu\text{mol/l}$	5	4
Age ≤ 25 , serum creatinine $\geq 130 \mu\text{mol/l}$	0	2
Age > 25 , serum creatinine $< 130 \mu\text{mol/l}$	0	0
Age > 25 , serum creatinine $\geq 130 \mu\text{mol/l}$	2	0
	3	2
Female patients		
Age ≤ 25 , serum creatinine $< 130 \mu\text{mol/l}$	5	24
Age ≤ 25 , serum creatinine $\geq 130 \mu\text{mol/l}$	3	4*
Age > 25 , serum creatinine $< 130 \mu\text{mol/l}$	1	4
Age > 25 , serum creatinine $< 130 \mu\text{mol/l}$	1	16
Age > 25 , serum creatinine $\geq 130 \mu\text{mol/l}$	0	1

* $p < 0.05$.

†Values are mean (SEM).

Table 5 Differences between patients with lupus nephritis developing renal failure and those maintaining life supporting renal function

	Renal failure	No renal failure
Number of patients (%)	8 (21)	31 (79)
Male patients	2	7
Age ≤25, serum creatinine <130 µmol/l	0	2
Age ≤25, serum creatinine ≥130 µmol/l	0	0
Age >25, serum creatinine <130 µmol/l	0	2
Age >25, serum creatinine ≥130 µmol/l	2	3
Female patients	6	24
Age ≤25, serum creatinine <130 µmol/l	2	5
Age ≤25, serum creatinine ≥130 µmol/l	1	3
Age >25, serum creatinine <130 µmol/l	3	15
Age >25, serum creatinine ≥130 µmol/l	0	1
Treatment		
Prednisone only	3	13
Prednisone + immunosuppressants	5	18

Figure 2 shows the chance of any patient with SLE in our study developing clinical signs of lupus nephritis. It shows that within the first three years after diagnosis of SLE a patient has a 30% chance of developing lupus nephritis, whereas after this time there is only about a 10% chance.

Figure 3 shows survival curves for patients with lupus nephritis according to serum creatinine concentration at the time of manifestation of the nephritis; survival of patients with initial serum creatinine values of $\geq 130 \mu\text{mol/l}$ was significantly

different from that of patients with normal ($<130 \mu\text{mol/l}$) initial serum creatinine values ($p<0.001$). When survival curves of patients with lupus nephritis with normal initial serum creatinine values were compared with those of patients without lupus nephritis there was a significant difference ($p<0.0001$), showing that patients with lupus nephritis and normal initial renal function have a worse prognosis than patients without nephritis and with normal renal function (data not shown).

INFLUENCE OF TREATMENT

Survival curves of patients with lupus nephritis (Fig. 4), divided according to treatment (prednisone ($n=16$) alone versus prednisone combined with

Fig. 1 Actuarial survival curves for patients with systemic lupus erythematosus with (—●—●) and without (—●—●) clinical renal disease ($p<0.001$).

Fig. 2 Actuarial survival curve, showing probability of survival without clinical renal disease in 110 patients with systemic lupus erythematosus (SLE) from the moment of SLE diagnosis.

Fig. 3 Actuarial survival curves for patients with lupus nephritis (LN), according to initial renal function with serum creatinine concentration greater (●—●) or less (●---●) than 130 μmol/l ($p<0.001$).

immunosuppressants ($n=23$), showed no difference between both groups ($p>0.05$); looking at the serum creatinine course, we could find no difference between these groups either (data not shown).

RENAL FUNCTION

Figure 5 shows the course of serum creatinine

Fig. 4 Actuarial survival curves for patients with lupus nephritis, according to treatment with prednisone (●—●) or a combination of prednisone with immunosuppressants (●---●) ($p>0.05$).

Fig. 5 Course of serum creatinine (S. creat) (mean (SEM)) from time of diagnosis of systemic lupus erythematosus (SLE) for patients without clinical renal disease (—*) and for patients with clinical renal disease maintaining life supporting renal function (●---●) or developing renal failure (●...●) with diagnosis of lupus nephritis as the starting point. $\dagger=p<0.05$ v patients without lupus nephritis; $\ddagger=p<0.001$ v other patients with lupus nephritis.

concentrations; it is clear that patients with SLE without clinical signs of lupus nephritis retained normal serum creatinine values (<130 μmol/l), whereas patients with nephritis had a more fluctuating and unpredictable course of serum creatinine. Patients prone to renal insufficiency reached this situation within a short period of time, while others recovered normal renal function; some of these patients ($n=8$) experienced a second renal exacerbation (mean period after first manifestation 60.2 (SEM 40.1) months) with reversible decrease in

Table 6 Demographic data on patients with systemic lupus erythematosus with clinical renal disease, according to the presence of hypertension

	Hypertensive	Normotensive
Number of patients (%)	24 (62)	15 (38)
Pre-existent	3	
At diagnosis of LN*	11	
In the course of LN	10	
Age at diagnosis of LN (years)†	33.8 (3.1)	33.5 (4.2)
Follow up (months)†	79.4 (10.2)	77.7 (14.6)
Median serum creatinine (μmol/l)	99.5	81
Number of deaths (%)	5 (21)	5 (33)
Number that progressed to dialysis (%)	6 (25)	2 (13)

*LN=lupus nephritis.

†Values are mean (SEM).

renal function, but all recovered normal serum creatinine values eventually.

SIGNIFICANCE OF THE OCCURRENCE OF HYPERTENSION IN THE DISEASE COURSE
Eight of 71 patients with SLE without lupus nephritis (11%) had hypertension compared with 24/39 (62%) of patients with lupus nephritis (Table 6) ($p < 0.001$). There was no difference between patients with lupus nephritis with or without hypertension in age at the moment of diagnosis for lupus nephritis, serum creatinine concentration, mortality, or need for renal replacement treatment.

Discussion

We studied 110 patients with SLE prospectively with special attention to clinically manifest renal involvement. Although clinical variables do not identify all patients with SLE with histological abnormalities of renal tissue,¹⁻⁵ they are thought to be good discriminating features for prognosis.^{8,9}

Our results show the presence of clinical manifestations of lupus nephritis in 39/110 (35%) of our patients with SLE; this is comparable with other recent findings,¹² but somewhat lower than previous figures.¹³ This probably reflects more frequent detection of milder cases of SLE in recent years. No significant sex difference was present, but patients with lupus nephritis were clearly younger than those without nephritis at the time of diagnosis of SLE.

The decreased survival (Fig. 1) associated with lupus nephritis is less pronounced than in earlier studies,^{14,15} probably reflecting better supportive care possibilities, but still stresses the fact that lupus nephritis is a major complication of SLE. Female patients with lupus nephritis under 25 years and male patients over 25 years had an increased mortality. Renal failure rates were not affected by age, sex, or initial serum creatinine concentrations, which is in contrast with current opinion.^{16,17} Initially normal renal function (serum creatinine $< 130 \mu\text{mol/l}$) in lupus nephritis did not lead to survival curves comparable with curves for patients with SLE without clinical renal disease. Thus the lupus nephritis itself was a risk factor for decreased survival, regardless of initial renal function. We could find no difference in survival according to treatment; in other studies, however, addition of oral immunosuppressants to prednisone did improve survival.^{18,19} Our study concerned a small number of patients and as the power of our test results is low ($\beta = 0.85$ for not detecting a 25% reduction in survival, while $\alpha = 0.05$) no firm conclusions about treatment can be drawn.

The chance of any patient with SLE in our study developing clinical renal disease was 30% for the three year period after the diagnosis of SLE (Fig. 2);

this means that patients with SLE surviving for more than three years without nephritis have a very low risk of developing clinical renal disease thereafter. The early use of corticosteroids did not influence the eventual occurrence of lupus nephritis. Although delayed onset nephritis has been described,²⁰ lupus nephritis mostly occurs early in the disease course of SLE.^{13,21}

Our finding that, regardless of treatment, those patients who will develop terminal renal insufficiency do so in a relatively short period after the diagnosis of lupus nephritis is made, is in accordance with other studies.²² The other patients with lupus nephritis maintained normal renal function and despite a renal exacerbation after four to five years in about 20% of patients normal renal function was maintained throughout the study.

The fact that patients with SLE without clinical renal disease conserve normal renal function seems obvious but has not been shown elsewhere; in view of the fact that they may well have histological abnormalities of renal tissue¹⁻⁵ and are at risk for vasculitis and drug induced damage it is reassuring that their survival (Fig. 2) and preservation of renal function (Fig. 1) are not influenced by other manifestations of SLE, and that clinical variables for lupus nephritis are excellent guides for management of patients with SLE.

Hypertension is an important complication and cause of subsequent loss of renal function in lupus nephritis; yet we could not find any relation between the presence of hypertension and severity of renal disease or disease course, which was found by others too.^{23,24} Probably, the possible deleterious effects of hypertension were recognised and properly treated, thereby eliminating its contribution to renal damage in our patients.

In conclusion, we have shown clinical renal disease to be present in 39 (35%) of our 110 patients with SLE, developing mostly within three years after the diagnosis of SLE, resulting in a decreased survival and increased morbidity compared with patients with SLE without clinical renal disease, who have an excellent prognosis. Survival after treatment of lupus nephritis with high dose prednisone or prednisone combined with immunosuppressants was equally good. Our findings indicate that clinical indices for renal involvement are excellent guides in the management and prognosis of patients with SLE; therefore, the routine use of renal biopsy in patients with SLE is not warranted.

We wish to thank P de Leeuw, R Smeenk, and C Hack for technical assistance, advice, and manuscript review and M Drinkwaard for secretarial assistance. This work was supported by a grant from the Dutch league against rheumatism (grant 86/CR/10).

References

- 1 Comerford F R, Cohen A S. The nephropathy of SLE. *Medicine (Baltimore)* 1967; **46**: 425-71.
- 2 O'Dell J, Hays R, Guggenheim S, Steigerwald J. Systemic lupus erythematosus without clinical renal abnormalities: renal biopsy findings and clinical course. *Ann Rheum Dis* 1985; **44**: 415-9.
- 3 Holcraft R, Dubois E, Lundberg G. Renal damage in SLE with normal renal function. *J Rheumatol* 1976; **3**: 251-61.
- 4 Mahajan S, Ordoner N, Feitelson P, Lim V, Spargo B, Katz A. Lupus nephropathy without clinical involvement. *Medicine (Baltimore)* 1977; **56**: 493-501.
- 5 Stamenkovic I, Favre H, Donath A, Assimacopoulos A, Chatelant F. Renal biopsy in SLE irrespective of clinical findings: long term follow-up. *Clin Nephrol* 1986; **26**: 109-15.
- 6 Karsh J, Klippel J H, Balow J E, Decker J L. Mortality in lupus nephritis. *Arthritis Rheum* 1979; **22**: 764-9.
- 7 Rosner S, Ginzler E M, Diamond H S, *et al.* A multicenter study of outcome in systemic lupus erythematosus. II. Cause of death. *Arthritis Rheum* 1982; **25**: 612-7.
- 8 Fries J F, Porta J, Liang M H. Marginal benefit of renal biopsy in SLE. *Arch Intern Med* 1978; **138**: 1386-9.
- 9 McCluskey R T. Value of renal biopsy in lupus nephritis. *Arthritis Rheum* 1982; **25**: 867-75.
- 10 Tan E M, Cohen A S, Fries J F, *et al.* The 1982 revised criteria for classification of SLE. *Arthritis Rheum* 1982; **25**: 1271-7.
- 11 Cohen A S, Reynolds W F, Franklin F G. Preliminary criteria for the classification of SLE. *Bull Rheum Dis* 1971; **21**: 643-8.
- 12 Wallace D J, Podell T E, Weiner J M, *et al.* Lupus nephritis. Experience with 230 patients in a private practice from 1950 to 1980. *Am J Med* 1982; **72**: 209-20.
- 13 Rothfield N, McCluskey R, Baldwin D. Renal disease in systemic lupus erythematosus. *N Engl J Med* 1963; **269**: 537-44.
- 14 Zweiman B, Karnblum J, Carnog J, Hildreth E A. The prognosis of lupus nephritis. Role of clinical-pathologic correlations. *Ann Intern Med* 1968; **69**: 441-62.
- 15 Baldwin D S, Lowenstein J, Rothfield N F, Gallo G, McCluskey R T. The clinical course of the proliferative and membranous forms of lupus nephritis. *Ann Intern Med* 1970; **73**: 929-42.
- 16 Austin H, Muenz L R, Joyce K. Prognostic factors in lupus nephritis: Contribution of renal histologic data. *Am J Med* 1983; **75**: 382-91.
- 17 Balow J. Lupus nephritis: natural history, prognosis and treatment. *Clin Immunol Allergy* 1986; **6**: 353-66.
- 18 Felson D T, Anderson J. Evidence for the superiority of immunosuppressive drugs and prednisone over prednisone alone in lupus nephritis. Results of a pooled analysis. *N Engl J Med* 1984; **311**: 1528-33.
- 19 Austin H A, Klippel J H, Balow J E, *et al.* Therapy of lupus nephritis. Controlled trial of prednisone and cytotoxic drugs. *N Engl J Med* 1986; **314**: 614-9.
- 20 Adelman D, Wallace D, Klinenberg J. Delayed onset of lupus nephritis. *Arthritis Rheum* 1987; **30**: 479-80.
- 21 Pollak V, Pirani C. *Dubois' lupus erythematosus*. Philadelphia: Lea and Febiger, 1987: 105-29.
- 22 Kimberley R P, Lockshin M D, Sherman R L. End-stage lupus nephritis. *Medicine (Baltimore)* 1981; **60**: 277-87.
- 23 Budman D R, Steinberg A D. Hypertension and renal disease in SLE. *Arch Intern Med* 1976; **136**: 1003-7.
- 24 Appel G, Cohen D, Pirani C, Meltzer J, Estes D. Long-term follow-up of patients with lupus nephritis. *Am J Med* 1987; **83**: 877-84.