Systemic lupus erythematosus with nephritis

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SUMMARY Thirty-six patients with the onset of symptoms of systemic lupus erythematosus before age 20 years (23 aged <15 years at onset) were studied during a 15-year period. All had clinical evidence of nephritis. They were followed for a mean of 5 years (range 6 months to 13 years) or until death. Survival was calculated to be 77% at 10 years for those aged less than 15, and 74% for those aged less than 20, from the onset of clinical nephritis. At referral, renal function was already impaired in two-thirds of patients. Renal biopsies showed mild focal or proliferative changes in 19% of patients, membranous lesions in 11%, and diffuse proliferative lesions in 70%. Three (8%) patients died during follow-up, all from sepsis, and 3 (8%) others required chronic haemodialysis for terminal renal failure. The prognosis even of severe lupus nephritis in childhood and adolescence has improved in recent years. Side effects of treatment remain an important cause of death and morbidity.

Early studies of children and adolescents with systemic lupus erythematosus (SLE) reported a high mortality,¹⁻⁶ and lupus nephritis was recognised as the major cause of mortality. Several studies¹⁻⁶ have suggested that the mortality in children was higher than in adults. More recently, further studies have reported the outcome of lupus nephritis in children and adolescents.⁵⁻⁹ Improving survival has been documented, and a recent paper suggests that children and adolescents with lupus nephritis may have a lower mortality rate than adults.¹⁰

The experience of 71 patients with lupus nephritis at Guy's Hospital up to 1977 has been recorded.¹¹ This paper describes children and adolescents with the onset of symptoms of SLE before 15 and 20 years of age, all with clinical evidence of nephritis, and compares the clinical features and prognosis with an equivalent group of patients aged over 20 years 'adults', from the same series of patients, up to the end of 1979.

Patients and methods

All patients discussed in this paper satisfied the preliminary criteria of the American Rheumatism Association¹² in that they showed at least 4 of the clinical criteria listed. All showed positive antinuclear factor tests, usually repeatedly, and (since 1972) a raised level of double-stranded deoxyribonucleic acid (ds-DNA) binding in their sera^{13 14} on at least one occasion, or a positive test using *Crithidia luciliae*.¹⁵ All patients had an adequate renal biopsy. All had been followed up for at least 6 months from onset, or until death or terminal renal failure, at 1 April 1980.

We excluded any patient with typical SLE and nephritis who did not have an adequate biopsy or follow-up; any patient with a probable diagnosis of lupus but who did not satisfy the strict clinical and immunological criteria; any patient with a clinical disease resembling SLE, but who had never shown evidence of circulating ds-DNA antibody; any drug-induced SLE.

Methods have been described previously.¹¹

Results

Onset data. The age of onset of symptoms of SLE varied between 7 and 19 years with a mean of 14 years. Two patients were younger than 10 years, 21 were between 10 and 14 years, and 13 were between 15 and 19 years at onset. Only one patient (aged 12) was a boy.

The dominant clinical feature at the time of initial presentation is shown in Table 1, although all patients showed more than one feature at onset. Even

Table 1 Main feature at presentation in 31* patients

	No*	(%)
Arthritis	16	(52)
Facial rash	5	(16)
Renal disease	4	(11)
Thrombocytopenia	2	(9)
Cerebral lupus	1	(5)
Pleurisy	1	(5)
Anaemia	1	(5)
Lymphadenopathy	1	(5)

In 5 patients there was lack of sufficient details of the initial illness. Only the main feature is listed.

in a group of patients chosen for the appearance of clinical renal disease, only 16% had renal disease as the main presenting feature.

The origins of the patients are shown in Table 2, and these are compared with the adults. Patients referred from abroad are excluded from the Table. Most of the patients had been born abroad (or had been born in the UK of parents born abroad). Eight of these 12 children were of West Indian origin.

The mode of presentation of renal disease in the children and adolescents was the nephrotic syndrome (in 22), and persistent proteinuria (in 14). In this they did not differ from adult onset patients. The mean time from onset of lupus symptoms to the onset of renal disease in the children was 3.1 years, although in 24 (67%) patients renal disease became evident one year or less after the initial symptoms. Three of the 22 nephrotic children also presented with early acute renal failure.

The glomerular filtration rate (GFR), measured at the first assessment at Guy's Hospital, a mean of 7 months from onset of renal symptoms, was below 80 ml/min per 1.73 m² in 23 (64%) patients.

The renal biopsy histological findings are shown in Table 3 and are compared with those of the adults. Details of the classification and biopsy appearances have been described.¹⁶ There was no difference between the child and adult onset cases.

The histological grade of the renal biopsy is related to the corrected GFR in Fig. 1. There was a trend for patients with more severe biopsy changes to have lower GFRs, with this trend becoming significant when grade 1 and grade 4 patients were compared.

Table 2 Origin and ages of patients

	<20 years	>20 years	Total
Total*	26	61	87*
Born in UK	14	49	63
Born abroad, or born to parents born abroad	12 (46%)	12 (20%)	24 (27%)

$\chi^2 = 6.4$; $P = 0.01$.

*Excludes referrals from abroad.

Table 3 Biopsy findings

Grade		Age at onset (years)			
		<10	10-15	16-19	>20
1	Minimal, mesangial, focal	0	6	1	16
2	Membranous	0	4	0	11
3	Proliferative glomerulonephritis, diffuse, irregular, with or without crescents	2	5	6	22
4	Proliferative glomerulonephritis, diffuse, severe, with or without crescents	0	6	6	17

Fig. 1 Lupus nephritis: glomerular filtration rate at time of biopsy, using a single-injection ⁵¹Cr edetate technique, for the different histological grades found on renal biopsy (see Table 3 for definition of grades 1-4).

Mean and SD of observations are shown. Differences were assessed using the *t* test.

The mode of presentation of renal disease is related to the histological grade of the renal biopsy in Table 4. Of the patients who presented with nephrotic syndrome, all but one had proliferative glomerulonephritis (grades 3 and 4) whereas of those who presented with proteinuria alone, 9 of 16 had minor or membranous changes (grades 1 and 2). This difference was highly significant. When patterns of deposition of immunoglobulin and complement were studied using immunofluorescence and immunoperoxidase techniques no difference in outcome was found between those classified as 'mesangial' deposits and those with deposits in the capillary wall.

Follow-up data. The most recent status of the patients is shown in Table 5. Mean follow-up from onset of lupus nephritis was 5 years (range 6 months to 13 years). Three (8%) patients died during follow-up, one from infection complicating pulmonary involvement, one from meningococcal meningitis, and one from sepsis associated with chronic renal

Table 4 Presentation related to histological grade

Presentation	Histological grade	
	1 and 2	3 and 4
Nephrotic syndrome	1	19
Proteinuria alone	9	7

$\chi^2 = 12.5$; $P < 0.001$.

Table 5 Most recent status of patients (n = 102)

Histological grade	No	Death other causes	TRF	CRF	PP	Remission
1	7	2	0	0	3	2
2	4	0	0	1	1	2
3	13	0	0	5	4	4
4	12	1	3	4	2	2
Age at onset (years)						
<10	2	0	0	0	1	1
10-14	21	2	2	2	9	6
15-19	13	1	1	8	0	3
>20 years	66	5	17	16	22	6

TRF = terminal renal failure—that is died of renal failure or needed dialysis or transplant. CRF = chronic renal failure with persistent proteinuria, GFR <80 ml/min per 1.73m². PP = persistent proteinuria, with or without a nephrotic syndrome, GFR >80 ml/min per 1.73m².

failure. Three (8%) patients presented in renal failure 14 months to 3 years after initial symptoms of lupus, and have continued on maintenance haemodialysis. Ten (28%) patients are in remission from nephritis (no proteinuria, GFR >80 ml/min per 1.73m²). Ten (28%) patients have persisting proteinuria but maintain their GFRs above 80 ml/min per 1.73m². Eleven (31%) patients are in chronic renal failure with GFRs below 80 ml/min per 1.73m². Ten of these patients had grade 3 or 4 histology on their initial renal biopsy.

The survival of the children from the onset of renal disease with the corresponding adult survival is shown in Fig. 2 calculated by the method of Cutler and Ederer.¹⁷ The standard error of each point and

Fig. 2 Lupus nephritis: actuarially calculated^{17 18} survival curves, and status at last follow-up, in patients with onset <15, <20, or >20 years of age. The survival curves of all those aged >15 and >20 years are indistinguishable, and thus a single survival curve is shown for the older patients.

Normal = normal renal function and urine; PP = persisting proteinuria, with or without a nephrotic syndrome, but a GFR of >80 ml/min per 1.73m²; CRF = chronic renal failure, GFR <80 ml/min per 1.73m².

the significance of the difference between the curves were calculated by the methods of Peto *et al.*¹⁸ The better survival in the children (onset <15) almost reaches significance ($P = 0.07$) and their latest status is significantly better than those with onset >15 years ($P < 0.03$ using the χ^2 test). Similar results were obtained when those over and those under 20 years were compared. Follow-up was similar (4.9 years for those with onset <20 years, 5.4 years for those with onset >20 years).

Four patients had repeat renal biopsies.

Treatment. All patients were treated with prednisone or prednisolone, and 32 were also treated with immunosuppressive drugs at some time, azathioprine ($n = 25$), cyclophosphamide ($n = 5$), azathioprine + cyclophosphamide ($n = 2$). More recently, 8 patients received courses of intravenous methylprednisolone 1 g daily for 3 days, and 3 patients received courses of plasmapheresis. Two patients were treated with dipyridamole and heparin, followed by warfarin, in addition to prednisone and azathioprine.

At the last follow-up (excluding the 3 dead patients), only 3 patients were on no immunosuppressive treatment, 9 were taking daily prednisone, 15 daily prednisone and an immunosuppressive (azathioprine in all but one), 1 alternate-day prednisone, and 5 alternate-day prednisone and azathioprine.

Discussion

Between 1963 and 1979, 102 patients of all ages with lupus nephritis were studied at Guy's Hospital. Thirty-six (35%) of these patients had the onset of symptoms of SLE before age 20 years and are the basis for this report. There was a pronounced female predominance, similar to most other paediatric series, but only 2 children were less than 10 years old at onset, and most were pubertal when their symptoms began.

Arthritis and skin rash were the predominant clinical features at presentation (Table 1) and it is worth noting that only 5 (16%) patients presented because of symptoms of renal disease. Renal disease was evident in 17 (64%) patients within one year, although this interval was as long as 14 years in one patient. An unexpected finding was the higher proportion of recent immigrants in the paediatric group (Table 2) since these patients had been drawn from the same local population as the adults. Eight of these 12 children were West Indian. The mode of presentation of the renal disease and the renal histology at the time of the first biopsy (Table 4), were similar to the adults. The initial assessment of

GFR indicated that the renal involvement had already progressed to impairment of renal function in 64% of the children by the time of referral. Since renal involvement had been recognised about 7 months before renal biopsy, this suggests that prompt referral might have reduced the proportion with renal impairment. Only those patients with grade 4 histology had significantly lower GFRs at presentation than those with lesser degrees of histological involvement (Fig. 1). In this series, the mode of presentation of the renal disease provided a reliable indication of the degree of histological involvement if a nephrotic syndrome were present (Table 4).

A 10-year survival rate of 87% for children and adolescents with focal glomerular lupus nephritis and a rate of 73% for those with diffuse proliferative lesions has been given.¹⁰ The data in Fig. 2 show 77% 10-year survival from onset of nephritis of all types in our children and adolescents. This was almost significantly better ($P = 0.07$) than the adult group, unlike earlier studies which suggested^{1,2} or demonstrated⁶ that survival in children was poorer than in adults. The most recent status was significantly better in the children and adolescents. All 3 deaths (Table 5) were the result of infection, and there was no correlation with the histological grade of the initial renal biopsy. However, 10 of the 25 patients with grade 3 or 4 histology at onset were in some degree of renal failure at most recent assessment. This compares with only 1 of 11 patients with grade 1 or grade 2 histology, but this trend did not quite reach significance in this small series. There was no correlation in the whole series¹¹ between initial histopathology and outcome. Most of our patients have had minor problems with arthralgia, rashes, thrombocytopenia, or Raynaud's phenomenon from time to time, but only one had a severe extrarenal manifestation of lupus, cerebrovascular complications. Contrary to some reports, all 3 of our patients on dialysis require anti-inflammatory treatment for arthralgia and rashes and we have chosen to use small doses of steroids for this. One patient has avascular necrosis of one hip.

Our treatment policy has been to use immunosuppressive drugs except for patients with minor focal or proliferative (grade 1) changes. In view of the fairly good long-term prognosis for membranous (grade 2) nephritis established in this and other series, we would not now use immunosuppressive therapy in these patients. At the start cyclophosphamide was used as an immunosuppressant agent but more recently azathioprine has been preferred¹¹ because of reports of bladder cancer during long-term cyclophosphamide treatment¹⁹ and because chemical cystitis was a problem in several patients.

The treatment of SLE nephritis is controversial, and has two aims. In patients with severe forms of nephritis, to prevent or (more commonly) to reverse deterioration in renal function; and in those with mild forms of nephritis, to prevent transformation into more severe forms of nephritis²⁰, as was noted in 2 of only 4 repeat biopsies done in this series. The first aim appears to have been achieved, in that in the majority of patients renal function improved and proteinuria diminished, which is rarely documented in untreated lupus, although controlled data are lacking. Some patients in whom the disease was slight, despite treatment with steroids, progressed to more severe disease. Whether more aggressive treatment would have prevented this change, we cannot say; certainly routine use of this more aggressive treatment in patients with mild disease and normal renal function would undoubtedly lead to an increase in the complications of the treatment, particularly sepsis.²¹ One of our patients with mild mesangial lupus glomerulonephritis died, with normal renal function and urine, of meningococcal meningitis, while taking prednisone and azathioprine.

The role of tests of activity (C3, C4, DNA binding, immune complexes) in the clinical management of lupus nephritis is a small one. Normal renal function may be maintained for long periods with abnormal complement and DNA binding studies,¹⁴ so that abnormal test results are not very useful. However, the finding of normal results permits safe reduction in drug dosage without exacerbation of disease, which is an important point in practical management.

The management of children and adolescents with SLE and nephritis remains difficult, and is best performed in conjunction with, or by, a specialist centre with experience of the many problems both disease and treatment may bring. Early referral may avert problems, in particular exacerbation of nephritis and a fall in GFR which is not always reversible by treatment. However, given careful—although still empirical—management, survival is good and morbidity low in a previously fatal disease.

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