LUPUS NEPHRITIS IN MALES AND FEMALES
I E Tareyeva, T N Janushkevitch, S K Tuganbekova
First Moscow Medical Setchenov Institute, Moscow, USSR

Summary

The course of lupus nephritis in 51 males was compared to that of 337 females. Nephrotic syndrome occurred with equal frequency in males and females, hypertension was more frequent in males, rapidly progressive lupus nephritis was much more frequent in males. The overall 10-year survival rate from the onset of systemic lupus erythematosus was 41 per cent in males and 60 per cent in females. The 10-year ‘renal survival’ – from the clinical evidence of renal disease to ‘renal death’ – was 40 per cent in males and 57 per cent in females. Thus the prognosis of lupus nephritis in males was worse than in females.

In 10 males and 65 females acetylation rate of sulfadimazine was studied. The predominance of slow acetylators was especially marked in males and in patients with more severe disease.

Introduction

The course of systemic lupus erythematosus (SLE) is greatly influenced by hormonal and genetic factors. The disease mostly affects sexually mature women and is relatively rare in males, though several families in which SLE predominates in males have been described [1]. Animal models, such as the inbred mouse, support the theory that sex hormones are important in the pathogenesis of SLE. In certain strains morbidity is greater in females, in others, such as BXSB mouse, the males have a lupus-like syndrome while there is little involvement in females.

There are few reports comparing the course of the disease in males and females and only a few discuss the course of nephritis. In one of the latest publications Wallace et al [2] report the clinical course of SLE in 609 patients, 209 of them with renal involvement; the 10-year survival of males with SLE is reported to be less than that of females, though survival rates between males and females with nephritis did not differ.

The statement of Wallace et al that their 230 lupus nephritis series represents
the largest single centre group ever described prompted us to report our experience.

Patient details

We have been observing 388 patients with SLE and clinical evidence of renal involvement admitted during a 25-year period (1958–1982) to the Clinic of Internal Medicine (mainly to its Renal Unit) of the Medical Sefchenov Institute. The mean follow-up period was 5.7 years. Here we present the data concerning the course of nephritis in 51 males and 337 females aged 15–60 years.

Clinical findings

The general clinical features in most patients resembled lupus as a whole, with multi-system involvement. All patients had positive LE-test and/or high titres of anti-DNA-antibodies, 28 patients (all females) presented with isolated renal disease, in three of them no systemic signs appeared during a mean follow-up of 3.6 years.

All patients had proteinuria (≥0.5g/L), 105 had nephrotic syndrome, 191 had arterial hypertension. Thirty-five patients had rapidly progressive lupus nephritis with nephrotic syndrome, severe hypertension and rapid deterioration of renal function. Renal biopsies were performed in 105 patients. In 34 patients diffuse proliferative lupus nephritis and in 35 mesangio-proliferative lupus nephritis was found; 12 patients had membranous lupus nephritis, 8 patients had membrano-proliferative lupus nephritis and in 15 patients predominantly sclerotic lesions were found.

The comparison of age of our male and female patients showed that lupus nephritis was very rare in males over 40. The ratio males: females was similar in all groups up to 40 years (15–20 years, 21–30 years and 31–40 years), being roughly 1:6; in patients over 40 it fell to 1:15 (2 males and 30 females).

The analysis of clinical features showed that the nephrotic syndrome occurred with equal frequency in males and females (27% and 32% respectively). Hypertension was more frequent in males (67% and 46%); three men (but no women) had myocardial infarction. Rapidly progressive nephritis was much more frequent in males (23.5% versus 6.7%). Regarding renal biopsy findings, the only difference concerned membranous lupus nephritis (all patients with this histological form were females); other histological forms were found with equal frequency in both groups of patients.

During the follow-up period 155 patients died – 26 of 51 males (51%) and 129 of 337 females (38%). In 63 per cent of patients death occurred from renal failure.

Assessing the course of disease in our patients we calculated life table analysis by the method of Cutler and Ederer. When calculating overall survival, the onset of disease was designated as time of first symptom of SLE. The 5-year survival rate of all 388 patients was 72 per cent, 10-year survival was 57 per cent and the 20-year survival was 34 per cent. Our series was not typical of lupus as a whole, but only of the subset with clinically evident nephritis. The survival of our
patients was a little less than the survival of a comparable group of Cameron [3] who in a series of 71 patients with lupus nephritis seen over a 15-year period reported a 10-year survival of 65 per cent.

The prognosis in males was worse than in females, 5-year survival being respectively 57 per cent versus 76 per cent, 10-year survival 41 and 60 per cent and 20-year survival 27 per cent and 40 per cent.

To assess the course of nephritis we calculated 'renal survival' (i.e. the 'survival of renal function'). For this purpose we took clinical evidence of renal involvement as our entry criterion, 'death' meant death from renal failure and included also the need for dialysis and transplantation, e.g. a serum creatinine \( \geq 8.5 \text{mg/dl} \).

Ten-year renal survival of all patients was 53 per cent, being 40 per cent in males and 57 per cent in females.

Thus prognosis of lupus nephritis in females was much better. The best prognosis was in women over 40 — none had rapidly progressive nephritis, only one patient in this group died of renal failure, the 10-year renal survival being 95 per cent. One of two older male patients had very benign course of lupus nephritis — after 15 years of renal involvement his serum creatinine is 0.8mg/dl, the other was lost to follow-up.

The treatment in both groups of our patients was similar: 33.3 per cent of men (17/51) and 34.4 per cent of women (115/337) received high dose cortico-steroids, 47.1 per cent (24/51) and 27.9 per cent (94/337) respectively received immunosuppressive drugs; 19.6 per cent (10/51) of males and 37.5 per cent (128/337) received only low-dose steroids. Thus, the difference in survival rates was not due to less intensive treatment of males.

In 75 patients (mainly Russians) we studied the acetylation phenotype by acetylation rate of sulfadimazine; 47 patients (62%) were found to be slow acetylators. Among patients with a more severe form of the disease 75 per cent were slow acetylators. Among 65 females, 38 (58.4%) were slow acetylators, among the 10 males only one was a rapid acetylator. Thus, there was marked predominance of slow acetylators in patients with more severe disease and in male patients.

References

1 Lahita RG, Chiorazzi N, Gibofsky A et al. Arthr Rheum 1983; 26: 39
3 Cameron JS. Q J Med 1979; 48: 1
Open Discussion

RITZ (Heidelberg) In addition to the explanation you gave for the paradoxical discrepancy between the course in males and females, let me add another one. We know that if we give anti-oestrogenic therapy both to experimental models such as the NZB/NZW mice and to females the course of lupus nephritis is attenuated. In contrast you show, and this is in agreement with other experience, that the course is more severe in males. I think another explanation would be genetic heterogeneity. We know that there are strains of mice, like BXSB mice, where males are more severely affected by a gene coded on the Y chromosome and other like the NZB/NZW mouse where males fare much better. I would like to offer as an additional explanation that this is evidence in the human of underlying heterogeneity of the lupus population.

TAREYeva It seems to me that you are speaking about the genetic differences between males and that there are several groups of males which are susceptible to this and to the other. Yes, we now study the genetic markers of disease. The first I cannot tell in detail but one thing I can say that men with red hair in our series rapidly died.

ABORAS (Jeddah) I have observed that in spite of the high prevalence of hypertension and cardiovascular disease as a presentation of lupus nephropathy in males, you have used more corticosteroid therapy than other types of drugs. I observed also that the survival rate was very bad. Is there any relation between the treatment and survival? Why have you used corticosteroids more than other types of drugs in such patients?

TAREYeva No, it was not so in our figures. There was no treatment particular to hypertensive patients. Certainly in hypertensive patients we prefer other types of drugs. Some work shows that the addition of cystostatic drugs improves prognosis. In very severe cases with rapidly progressive nephritis we always use high dose corticosteroids with cystostatic drugs and with heparin. We still use high dose steroids even in patients with hypertension if they are the cases with rapidly progressive nephritis.

DAL CANTON (Naples) I suppose that many of your female patients became pregnant while they were under your observation. It could be of great interest for us to know whether the disease influenced the course of the pregnancy and on the other hand whether pregnancy influences the course of the disease?

TAREYeva This is a very interesting question. I am not sure whether I can present all the data now as I am unprepared for the question. But 35 to 40 of our patients have been pregnant and certainly in half of them the pregnancy aggravated the course of the disease but nearly 20 to 25 had normal births and we have now under observation 20 to 23 children and they are unaffected. Some of them were retarded in their first year.
GOLDSMITH (Liverpool) Do you think that the influence of acetylator status on prognosis arises through its influence on the disease, or through the influence on the metabolism of the drugs used in the treatment of the disease?

TAREYEVA No, I think it is the influence on the disease itself by a genetic predisposition.

DAVISON (Chairman) Following from Dr Goldsmith's question did any of the slow acetylators have their lupus precipitated by some drug exposure chemical exposure or anything you could detect?

TAREYEVA No, not in these patients.

SCHEMA (Chairman) Have you compared the percentage of hypertension in male patients with SLE and in male nephritis patients without SLE?

TAREYEVA I do not think there is any difference.