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FACTORS AFFECTING THE PROGRESSION OF IgA NEPHRITIS

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Summary

One hundred and fifty-one patients with IgA nephritis were studied to determine prognostic features. Mean duration of follow-up was 50±34 months (range 6 to 168 months). The patients with progressive disease (14%) either followed a slow course reaching end-stage renal failure in an average of 7.7 years or a more rapid decline with an average of 3.3 years, due to severe uncontrolled hypertension. The cumulative renal survival was 91 per cent after six years with no further development of renal failure up to 14 years. Unfavourable prognostic indices were proteinuria exceeding 2g/24 hours, hypertension, glomerular crescents on biopsy, severe segmental sclerosis and medial hypertrophy of renal blood vessels.

Introduction

Although the majority of patients with IgA nephritis have a benign course [1–3] there have been increasing reports of patients developing end-stage renal failure after a follow-up period of a few years [4–6].

This is a study of the natural history of IgA nephritis where the patients were seen early because of routine screening. An attempt was made to identify and determine prognostic features and among those with progressive disease the reciprocals of their serum creatinine were plotted serially with time to document the evolution of their renal deterioration.

Material and methods

One hundred and fifty-one patients with biopsy proven IgA nephritis were studied. Percutaneous renal biopsies were performed using a modified Vim Silvermann needle. Specimens containing less than 10 glomeruli were not included. Mesangial IgA nephritis was defined histologically as an enlargement of the

mesangial area either by mesangial cell or by increase in mesangial matrix (in the absence of thickening or double contours of glomerular capillary walls) on light microscopy, IgA deposits (as the sole or predominant immunoglobulin) in the mesangial area on immunofluorescence and demonstration of electron-dense deposits in the mesangium by electron microscopy. Liver disease, systemic lupus erythematosus and Henoch-Schönlein purpura were excluded in all patients.

Blood pressure measurements, urine analysis, quantitative protein excretion and serum creatinine concentrations were analysed in all cases. Serum complement and immunoglobulins were also measured.

Reciprocals of creatinine The change in the reciprocal of the serum creatinine (1/Cr) with time was chosen to describe the progression of renal impairment in our patients as the predictability of a linear decline in 1/Cr with time is well established [7].

Patients Of the 151 patients in the study, 110 (73%) were males and 41 (27%) were females. Their mean age was 27±6 years and duration of follow-up 50±34 months (range 6 to 168 months). Ninety-eight (65%) were detected by routine screening and the other 53 (35%) were referred because of symptoms or because of hypertension or renal impairment. None of the patients, apart from the ones with nephrotic syndrome, received any treatment during the follow-up period, other than hypotensive medication where indicated.

Statistics Results are expressed as mean ± standard deviation (SD). Statistical analyses were performed using Student's 't' test, χ^2 test and linear correlation coefficients.

Results

Clinical presentation At presentation, 66 per cent had asymptomatic haematuria and proteinuria of which 82 per cent (81 of 99) were males; 24 per cent (36 of 151) had gross haematuria and proteinuria, four per cent (6 of 151) had the nephrotic syndrome, five per cent (8 of 151) had renal impairment (serum creatinine >1.6mg%) [8].

Histopathology Eighty-seven per cent had diffuse proliferative glomerulonephritis, 89 per cent had associated glomerulosclerosis and 25 per cent associated crescents.

Immunofluorescent studies showed IgA alone in 68 per cent, IgA and IgG in 14 per cent, IgA and IgM in four per cent. Eighty-nine per cent had C_3, 30 per cent had fibrin and nine per cent C1q. Two patients had C_4.

Clinical course. Initial renal function at biopsy In 59 patients the serum creatinine was <1mg/dl, 84 between 1 to 1.6mg/dl and eight patients had a serum creatinine greater than 1.6mg/dl.

Progression to renal failure Of those with a serum creatinine less than 1mg/dl, one had renal impairment and two developed end-stage renal failure (serum

creatinine >10mg/dl). In the group with serum creatinine between 1 and 1.6mg/dl there were nine with renal impairment and two with end-stage renal failure; of those with a serum creatinine >1.6mg/dl there were three with renal impairment and five with end-stage renal failure.

At the end of the follow-up period, 86 per cent (129 of 151) had stable function (Group A), while nine per cent (13 of 151) had slow deterioration with renal impairment (Group B) and five per cent (9 of 151) progressed to end-stage renal failure (Group C).

Some with initial normal renal function progressed to end-stage renal failure within three years while others had reached an abnormal serum creatinine after five years of follow-up. None who were normal at six years showed subsequent deterioration.

Among the patients with end-stage renal failure severe uncontrolled hypertension was a possible cause for rapid deterioration in seven. In another patient we documented pregnancy as a cause for rapid deterioration. The remaining patient presented with nephrotic syndrome with renal impairment and crescents on biopsy. He did not have hypertension, thus he could have developed a superimposed crescenteric glomerulonephritis.

Extrapolation of the slopes of 1/creatinine against time in patients with slow deterioration and those with rapid deterioration to end-stage renal failure to a common starting point shows that on average they developed end-stage renal failure in 7.7 and 3.3 years respectively. Life table analysis of the cumulative survival of the 151 patients showed that 91 per cent of the patients had normal function at six years with no further development of renal failure up to 14 years.

Prognostic features The incidence of possible prognostic factors in the three groups of patients (A, B, C) was analysed.

Proteinuria More patients with end-stage renal failure (Group C) had proteinuria exceeding 2g/24 hours when compared with those in Group A (patients with stable renal function), $\chi^2=10.9$ ($p<0.01$). Of those with the nephrotic syndrome (6 patients), three with selective proteinuria remitted either spontaneously or after treatment, two persisted (with non-selective proteinuria) and one developed end-stage renal failure (selectivity not measured).

There were 34 of 151 patients (23%) with hypertension; mean age 28±9 years with a follow-up of 55±39 months. Patients in Groups B and C had significantly higher incidence of hypertension compared with group A ($p<0.001$). There was no difference between B and C.

Crescents Patients with end-stage renal failure (Group C) had significantly more crescents on renal biopsy when compared to those with stable renal function (Group A), $\chi^2=19.6$, $p<0.01$). There was, however, no difference between B and C or between A and B.

Glomerulosclerosis There was no significant difference in the distribution of global sclerosis between patients with normal renal function and those with end-stage renal failure. However, patients with clinical resolution of the disease

had significantly less segmental sclerosis compared to those with end-stage renal failure (6 of 13 versus 8 of 9, $\chi^2=4.2$, $p<0.05$). Segmental sclerosis correlated with crescents ($r=0.36$, $p<0.01$), proteinuria ($r=0.44$, $p<0.001$) and medial hypertrophy of blood vessels ($r=0.48$, $p<0.001$). Global sclerosis was not correlated with crescents and the correlation with proteinuria ($r=0.22$, $p<0.05$) and medial hypertrophy ($r=0.4$, $p<0.01$) was less.

Medial hypertrophy 17.7 per cent of those with medial hypertrophy as opposed to 1.7 per cent without medial hypertrophy had renal impairment ($\chi^2=12.7$, $p<0.0005$) on presentation. On follow-up, the overall incidence of renal failure was 29 per cent (10 of 35) in patients presenting with medial hypertrophy. Of those 10 patients with renal failure, three had no hypertension, another three had medial hypertrophy and renal impairment before the development of hypertension and the remaining four patients had medial hypertrophy associated with renal impairment and hypertension at presentation.

There was no difference in age, serum IgA or tubular atrophy between the three groups, although the severity (grade mild, moderate, severe) of the tubular atrophy was significantly greater in group C than group A (3 of 9 versus 3 of 129, $\chi^2=18.6$, $p<0.01$).

Discussion

National service is compulsory in Singapore and all young males upon attaining the age of 16 are screened prior to induction into the armed forces. Those found to have urinary abnormalities are referred to us for further investigations. This also explains the male preponderance among the patients detected by screening (only 15 females were detected by screening).

The rest of the 53 patients (27 males and 26 females) came to us seeking advice because of various symptoms. This group probably reflects the clinical features of most published series where patients are diagnosed later.

Among the 151 patients, 86 per cent had stable renal function, nine per cent had slow deterioration of renal function with renal impairment and five per cent progressed to end-stage renal failure during a follow-up period of 50±34 months (range 6 to 168 months). Ninety-one per cent of patients still had normal renal function at six years, indicating the benign course of the disease.

Reciprocal transformation of the serum creatinine enables the course of renal failure to be viewed at a glance [9,10]. Our patients with IgA nephritis, when they develop renal impairment, run two different courses. One, slowly progressive, probably represents the natural history of deterioration in renal function due to the nephritis. The other is more rapid where progression to renal failure occurs in a few years and where severe uncontrolled hypertension seems to be the major adverse factor.

A comparison of the various factors which might have influenced the patients' clinical course showed that those who developed renal failure had more proteinuria, crescents, a higher incidence of hypertension, segmental sclerosis and medial hypertrophy of blood vessels compared to those with stable renal function.

Medial hypertrophy was associated with a significant incidence of renal impairment. Sixty per cent of those patients (6 of 10) either did not develop hypertension or developed it after the onset of renal impairment. Thus it would appear that in some patients, medial hypertrophy is a reflection of renal disease and not of hypertension.

The incidence of nephrotic syndrome in our series was only four per cent. These patients seemed to behave in a similar manner to patients with nephrotic syndrome due to other causes where the presence of selective proteinuria is associated with response to treatment. We have studied protein selectivity in IgA nephritis and found that patients with poorly selective proteinuria were more likely to have poor prognostic features such as renal impairment, hypertension and severe glomerulosclerosis.

References

1 Lim CH, Woo KT, Pwee HS et a. In *Proceedings of 2nd Asian Pacific Congress in Nephrology, Melbourne.* 1983: 175–182
2 Levy M, Beaufils H, Gubler MC et al. *Clin Nephrol 1973; 1:* 63
3 Joshua H, Sharon Z, Gutglas E et al. *Am J Clin Path 1977; 67:* 289
4 Hood SA, Velosa JA, Holley KE et al. *Clin Nephrol 1981; 16:* 55
5 Kobayashi Y, Tateno S, Hiki Y et al. *Nephron 1983; 34:* 146
6 Frasca GM, Vangelista A, Biagini G et al. *Kidney Int 1982; 22:* 184
7 Knapp MS. *Kidney Int 1983; 24:* 433
8 Chua KS, Jacob E, Lam CWK et al. *Singapore Med J 1978; 19:* 205
9 Mitch WE, Walser M, Buffington GA et al. *Lancet 1976; ii:* 1326
10 Rutherford WE, Blondon J, Miller JP et al. *Kidney Int 1977; 11:* 67