Long term follow up of renal function in IgA nephropathy

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Abstract

Fifty one children with IgA nephropathy verified at biopsy have been followed up clinically and functionally for 0.4-16.8 years from the onset of symptoms. Renal function was evaluated by determining the glomerular filtration rate (GFR) and effective renal plasma flow (ERPF) from the clearances of inulin and para-aminohippuric acid. Fifteen (29%) of the children had raised serum creatinine concentrations at the onset. Mean GFR was significantly lower than that of controls at the first investigation. During the follow up GFR and ERPF decreased and were significantly lower than in the controls after eight years of disease. The significant fall in renal function was found in children with proteinuria and especially in boys, in whom GFR and ERPF decreased from a mean (SEM) of 117 (5) and 616 (31) at 2.8 years to 97 (6) and 509 (36) ml/min/1.73 m² at 7.5 years. Patients with raised serum creatinine concentrations at the onset had significantly lower GFRs, and patients with macroscopic haematuria at this time did not show decreased renal function at follow up.

In conclusion, children with IgA nephropathy do not seem to have a benign clinical course. Boys with proteinuria show a significant decrease in renal function during follow up.

IgA nephropathy was once regarded as a benign kidney disease, especially in childhood.¹⁻³ It is now apparent that a certain percentage of cases progress to renal failure.⁴⁻¹¹ Early onset of disease is considered a benign sign,^{3 12 13} while proteinuria is claimed to be a marker of poor prognosis.^{6 10 11 14 15} It has also been shown that males generally have a poorer prognosis than females.^{10 14 16 17} There are few long term follow up studies of juvenile IgA nephropathy, particularly regarding renal function.^{1 18-20} Most of these studies find no persistent reduction of glomerular filtration rate (GFR). Thus Michalk *et al* concluded that a permanent decrease in renal function seems to be exceptional during childhood.¹⁹ The observation periods in all these series were short so Michalk *et al* conclude that prospective long term studies with regular clearance measurements are necessary for a better evaluation of the prognoses of children with IgA nephropathy. Thus the aim of the present study was to follow up renal function regularly in a group of patients with IgA nephropathy that has been verified by biopsy with an onset of disease during childhood and to relate functional changes with clinical symptoms.

Patients and methods

Renal function was examined in 51 children (30 boys and 21 girls), 3-18 (median 13) years of age when first functionally investigated, who had IgA nephropathy verified at biopsy and who had no signs of systemic diseases such as systemic lupus erythematosus, Henoch-Schönlein purpura, or liver disease. Renal function was evaluated regularly at intervals of about two to three years based on the GFR and effective renal plasma flow (ERPF). All renal function tests were performed with the patients in stable condition without signs of current infection. The follow up period from the first appearance of symptoms ranged between 0.4 and 16.8 years with a mean of 6.5 years. Twelve patients were followed for more than 10 years from the onset of symptoms.

GFR and ERPF were determined from the clearances of inulin and para-aminohippuric acid during water diuresis, using a standard clearance technique including continuous infusions of inulin and para-aminohippuric acid after a priming dose.²¹ Four 30 minute urine samples were collected by spontaneous voiding and the clearance values presented are the means of the four clearance periods.

Patients with proteinuria are those who show proteinuria on several occasions when in stable condition in between acute infections. As the investigation has been done during a 10 year period, the determinations of small amounts of albumin in urine was not performed during the first years. Proteinuria is therefore defined as a positive Albustix (Ames) test or urine albumin/creatinine ratio >10 (mg/mmol) in short term urine samples collected in the morning at 74 of the 134 renal function tests.

Inulin in blood and urine was analysed by the anthrone method²² and para-aminohippuric acid by a modified technique of Smith *et al*.²³ Urine albumin concentration was determined by an automated immunonephelometric method (Behring Nephelometer Analyser).

The results were compared by means of the Mann-Whitney non-parametric test and paired *t* test and the results are presented as mean (SEM). The renal haemodynamic data are compared with those of 36 healthy children (16 boys and 20 girls), 3.5-20.5 (median 12.5) years of age.

Results

CLINICAL PRESENTATION

Figure 1 shows the distribution of patients with IgA nephropathy by age and sex at clinical presentation. The first symptoms were discovered at a significantly earlier age in girls than boys (7.1 (0.8) compared with 10.7 (0.6) years).

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Figure 1 Age at onset and sex distribution for all children studied.

Fifteen (29%) out of 51 patients (nine boys, six girls) showed increased serum creatinine concentrations at the onset of the first symptoms. When these 15 children were first investigated with renal function tests, the GFR of five of them had already returned to normal, while the rest still had significantly ($p<0.001$) reduced GFR, ERPF, and filtration fraction (with means of 79 (5), 522 (21) ml/min/1.73 m² and 15.3 (1.1) % in comparison with the onset of the disease progressed to terminal renal failure with GFRs of 66, 32, and 13 ml/min/1.73 m² at 1.4, 2.1, and 2.4 years from the onset. This girl received a renal transplant 2.6 years after the onset of the disease. The other three patients all had persistent proteinuria.

Macroscopic haematuria as a first sign of the disease was found in 22 (43%) of the 51 children, and significantly ($p<0.05$) more often among boys (17/30, 57%) than among girls (5/21, 24%). In later episodes 38 of the 51 patients (75%), 24 boys (80%) and 14 girls (67%), showed macroscopic haematuria.

Table 1 Renal haemodynamic data on the 51 children with IgA nephropathy at the first investigation in comparison with 36 healthy children (controls). Results are mean (SEM)

	IgA nephropathy (n=51)	Controls (n=36)
GFR (ml/min/1.73 m ²)	108 (3)*	119 (2)
ERPF (ml/min/1.73 m ²)	602 (15)	627 (14)
Filtration fraction (%)	18.3 (0.5)	19.2 (0.4)

*Indicates significant ($p<0.05$) difference between the groups.

Hypertension did not occur at the onset in any child, but three children developed hypertension during follow up. All three of these children had reduced renal function at the onset, the girl with the nephrotic syndrome at the onset and two other boys with proteinuria as well. The disease progressed in all three during follow up, and in the girl to terminal renal failure.

Serum IgA concentration was determined in 49 children. Twenty three (47%; 57% of the boys and 33% of the girls) of these children had values above the normal for their ages.

RENAL HAEMODYNAMICS

Table 1 shows the mean GFR, ERPF, and filtration fraction of the whole group in comparison with 36 healthy controls. The first renal function test selected here does not include the very first test performed in the patients with reduced GFRs when first investigated. In these patients the second investigation was chosen, when GFR had returned to normal or nearly normal. GFR was significantly decreased in the children with IgA nephropathy compared with the controls. ERPF and filtration fraction did not differ between the patients and the controls.

Figure 2 shows the GFR and ERPF of all patients at different periods of time from the onset of disease. GFR during the first two years (111 (3) ml/min/1.73 m²) as well as after more than eight years' duration of disease (107 (3) ml/min/1.73 m²), was significantly lower than that

Figure 2 (A) GFR and (B) ERPF in individual patients during follow up in different time periods from the onset of the disease. The stars above the symbols indicate significant differences calculated by the paired t test and the stars below the symbols indicate significant differences calculated with the non-parametric Mann-Whitney test; * $p<0.05$, ** $p<0.01$, and *** $p<0.001$.

of controls. A significant fall (paired *t* test) in GFR was found from five to eight to more than eight years. ERPF did not differ significantly from that of controls during the first years but was significantly lower than that of controls after five years' duration of disease. A significant decrease in ERPF, calculated by paired *t* test, was seen from about eight years' duration of disease. Filtration fraction increased from the first two years to after five years' duration of disease.

Table 2 shows the first and last renal haemodynamic values for the 38 patients studied on more than one occasion. The first study was chosen when the initial reduction in renal function, found in some patients, had been overcome. GFR and ERPF decreased significantly during follow up to values significantly lower than those of controls. When the patients are grouped according to sex (table 2), boys show decreases in their GFR and ERPF to values significantly lower than those of controls. Girls, however, had a significantly lower GFR (113 ml/min/1.73 m²) than that of controls from the beginning, but did not decrease their GFR further during follow up.

When the patients are grouped into those with and without proteinuria during follow up (table 2) and the nephrotic girl, whose condition progressed to terminal renal failure is excluded, the GFR and ERPF of those patients with proteinuria decreased significantly during follow up. Patients without proteinuria show no progression and have a normal GFR and ERPF throughout the follow up period. After a further grouping of the patients according to sex as well

Table 2 Renal haemodynamic data on the 38 patients investigated more than once (that is, 2–6 times). Results are mean (SEM) and for GFR and ERPF in ml/min/1.73 m²

	First investigation	Last investigation
All patients (n=38)		
Time from onset (years)	3.2 (0.5)	7.8 (0.6)
GFR	114 (2)***	105 (4)§§§
ERPF	594 (16)**	542 (21)§§
Boys (n=22)		
Time from onset (years)	2.4 (0.5)	6.8 (0.7)
GFR	117 (3)**	106 (4)§§§
ERPF	607 (20)*	551 (25)§§§
Girls (n=15)†		
Time from onset (years)	4.4 (0.8)‡	9.7 (1.0)‡
GFR	113 (3)§	109 (4)§§
ERPF	580 (26)	562 (21)§
Boys and girls with proteinuria (n=17)†		
GFR	115 (4)***	100 (4)§§§§
ERPF	604 (26)***	519 (28)§§§§
Boys and girls without proteinuria (n=20)		
GFR	116 (2)	114 (3)¶¶
ERPF	589 (19)	586 (17)¶
Boys with proteinuria (n=12)		
GFR	117 (5)***	97 (6)§§§§
ERPF	616 (31)***	509 (36)§§§§
Boys without proteinuria (n=10)		
GFR	118 (4)	116 (3)¶¶
ERPF	597 (24)	601 (27)
Girls with proteinuria (n=5)†		
GFR	111 (7)	105 (6)§§
ERPF	577 (53)	543 (48)§
Girls without proteinuria (n=10)		
GFR	114 (3)	111 (5)§
ERPF	581 (31)	571 (21)

†The girl with the nephrotic syndrome excluded.

‡Significantly (*p*<0.05) different from the boys.

p*<0.05, *p*<0.01, ****p*<0.001, difference between first and last investigation by paired *t* test.

§*p*<0.05, §§*p*<0.01, §§§*p*<0.001, significantly different from that of controls by paired *t* test.

¶*p*<0.05, ¶¶*p*<0.01, significantly different from those with proteinuria by paired *t* test.

Table 3 Last renal haemodynamic data on the patients with an initially raised serum creatinine concentration in comparison with those with normal serum creatinine concentrations at the onset. Results are mean (SEM)

	Raised creatinine at onset (n=15)	Normal creatinine at onset (n=36)
Duration of disease (years)	4.6 (1.0)*	7.2 (0.7)
GFR (ml/min/1.73 m ²)	98 (8)**	110 (2)
ERPF (ml/min/1.73 m ²)	538 (47)	580 (18)
Filtration fraction (%)	18.1 (0.7)	19.5 (0.5)

p*<0.05 and *p*<0.01 indicate a significant difference between the groups.

as to the occurrence of proteinuria, boys with proteinuria are the patients whose GFR and ERPF decrease during follow up to values significantly lower than those of controls. Girls with proteinuria have a significantly lower GFR and ERPF than controls at the last investigation, but, by the paired *t* test, no significant decreases were seen from the first to the last investigation. Neither boys nor girls without proteinuria showed any changes in renal function during follow up.

Table 3 gives the last renal haemodynamic data on the 15 patients with increased serum creatinine values at the onset of the disease in comparison with the 36 patients who did not show raised serum creatinine concentrations in their first episode. Patients with signs of acute nephritic syndrome at the onset, that is, raised serum creatinine concentration with haematuria and/or proteinuria, seem to have a poorer prognosis, with a lower GFR despite a shorter follow up period.

Renal function in patients with macroscopic haematuria at the onset did not differ from those without macroscopic haematuria either at the first or last renal function investigations. Nor was there any difference in renal function at the first or last investigation in those with raised or normal serum IgA concentrations.

Discussion

There are few long term follow up studies of patients with a clinical onset of IgA nephropathy during childhood.^{19 20 24 25} In adult as well as in most childhood studies there is a male preponderance,^{2 3 12 14 16 25 26} although Kusumoto *et al* report a rather similar distribution between the sexes in juvenile in contrast to adult onset IgA nephropathy.¹³ In the present study the ratio of males to females is about 1.5:1. Furthermore, the disease seems to present at an earlier age in girls than in boys. This has not been reported explicitly previously,^{16 17} but it also seems to occur even in another report on childhood IgA nephropathy.²⁴ The question is whether or not the disease has an earlier onset in girls. As urinary tract infections are much more common in girls,²⁷ more urinalyses may be performed in them than in boys in connection with uncertain disorders and result in an earlier detection of asymptomatic patients among girls. This possibility is further supported by the fact that the presenting symptoms in girls are more often microscopic haematuria and proteinuria, while macroscopic haematuria is found significantly more often as the symptom of onset

among boys. This higher frequency of macroscopic haematuria in males has also been found by others.^{1 5 16} Furthermore, gross haematuria seems to occur much more often among children than among adults.^{1 3 12 16 19 24} In the present study macroscopic haematuria did not seem to be related to a poorer prognosis as the last renal functional data did not differ between patients with or without macroscopic haematuria, as has also been found by others.^{5 6 9 11 17} Australian studies found significantly worse renal function in adults with a history of macroscopic haematuria,^{16 28} however, which was also found by Linné *et al* in juvenile onset IgA nephropathy.²⁰

In this study raised serum IgA concentrations were found in 47% of the patients, which is in line with other reports.^{13 17 23} Kher *et al*³ and Michalk *et al*¹⁹ found much lower frequencies and concluded that serum IgA did not appear to be a diagnostic test of IgA nephropathy in children.³ This is in contradiction to Kusumoto, who found a similar frequency in children to that in adults, that is, about 35%.¹³ Nor did they find any correlation between serum IgA concentration and the prognosis, which is well in line with the findings of the present study and other ones.^{5-7 9 14 16} Droz, however, reported a more favourable outcome in patients with higher serum concentrations of IgA,⁴ but in a later report he claimed that serum IgA concentrations had no prognostic significance.¹⁷

The rather high frequency of 29% of children with raised serum creatinine values at the onset is in good accord with the findings of other studies,^{5 8 14 16 20} but this was not seen by Kher,³ and in only a few cases by Lévy *et al*.¹ Hood *et al*¹⁴ and Nicholls *et al*¹⁶ found it more often in males, which was not found in the present study. This acute nephritic syndrome is usually reversible.^{5 24} In the present study GFR returned to normal in two thirds of the patients during follow up, and in one third it progressed. Hood *et al* reported progression in about half of the patients and regression in the other half.¹⁴ A long term follow up of renal function in these patients with raised serum creatinine at the onset showed a lower GFR in comparison with those with normal serum creatinine concentrations at the onset, and this finding is supported by Hood *et al*.¹⁴

In the initial renal functional data on the group of patients with raised serum creatinine values at the onset, the GFR, ERPF, and filtration fraction were significantly reduced. The low filtration fraction indicates a more reduced GFR than ERPF, which might support the hypothesis of relative hyperperfusion of a reduced number of functioning nephrons. The tendency of a relative hyperperfusion seems to remain during the first four years of the disease, after which time the ERPF goes down as well. Very few studies on renal function have been made with a special emphasis on determinations of renal plasma flow. Linné *et al* found super-normal GFRs ($>+1$ SD of those of controls) in seven out of 15 patients studied five to 17 years after the onset, but clearance of para-aminohippuric acid was within normal limits.²⁰

As in other studies,^{1 4-6 15} the nephrotic syn-

drome at clinical presentation was an infrequent finding. The prognosis in patients with heavy proteinuria seemed to be worse, however. This was also the case with the girl with the nephrotic syndrome in this study, who was the only one whose disease progressed to terminal renal failure within the short period of 2.6 years. The fact that proteinuria is associated with a poor prognosis is shown in this study as in other ones.^{5 9 10 11 14-17 24} Chida *et al* found a significant decrease in the renal survival rate in patients with proteinuria of more than 1 g/day and the most unfavourable prognosis in those with heavy proteinuria.¹¹ Clarkson *et al* point out that progressive disease becomes more manifest in the older proteinuric patients.⁵ In another study, where we explicitly examined renal function in relation to urine protein excretion, without the aspect of long term follow up, we found that patients with microalbuminuria had a reduced GFR, indicating that even microalbuminuria is a marker of progressive disease.²⁹

The present results also show that male gender is more frequently correlated with deterioration of renal function, as has been demonstrated by others.^{10 14 16 17 24} Droz found no differences between the sexes.⁴ In the present study girls with proteinuria had a decreased GFR and ERPF at the last renal function investigation, but they did not show a significant decrease from the first to the last examination. This might be due to the rather low number of girls with proteinuria studied. Girls have been reported to have a higher incidence of mild glomerular changes,²⁴ but that study did not demonstrate any difference between the sexes in GFR, proteinuria, and the incidence of hypertension, that is, in the clinical outcome. The follow up time was rather brief, however, with a mean of 3 years 4 months.

In summary several earlier reports have stressed the benign clinical course of IgA nephropathy with an onset of disease during childhood, but this long term follow up study of renal function has shown that children with IgA nephropathy and proteinuria, especially boys, have a poor prognosis. Patients with raised serum creatinine concentrations at the onset also seem to develop renal dysfunction as well as do the few children with hypertension in connection with IgA nephropathy.

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