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Clinical course and prognostic factors of clinically early IgA nephropathy

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ABSTRACT

Background: Immunoglobulin A nephropathy (IgAN) is prevalent in many countries including China. At the time of diagnosis many IgAN patients present with normal renal function, proteinuria of 0.4 g/d or less, and normal blood pressure and they are classified as clinically early IgAN patients. However, the natural history of clinically early IgAN and prognostic factors has not yet been clarified.

Methods: We investigated 177 early IgAN patients (108 males and 69 females) followed up for a mean period of 111 ± 43 months.

Results: During the follow-up period among 177 clinically early IgAN patients, urinary abnormalities disappeared in 9% of the patients; increased proteinuria was present in 79 patients (46%). The prevalence of hypertension was 38% (68 patients), and 24% (43 patients) developed renal insufficiency. Poor renal outcome was associated with haematuria, urinary protein excretion index (UPEI, the product of urinary protein excretion at the time of renal biopsy and prebiopsy duration), and tubulointerstitial lesions.

Conclusion: Renal outcome is dismal in patients with clinically early IgAN. Haematuria, UPEI, and tubulointerstitial lesions could be useful markers of a progressive course.

KEYWORDS

IgA nephropathy, histological lesion, proteinuria, renal progression

BACKGROUND

Primary immunoglobulin A nephropathy (IgAN) is the most prevalent glomerular disease throughout the world. At the time of diagnosis many patients with IgAN present with normal renal function, a proteinuria of 0.4 g/d or less, and normal blood pressure, and these patients are classified as clinically early IgAN patients.[1-4] In the absence of progressive factors such as renal insufficiency, heavy proteinuria, and hypertension, patients with clinically early IgAN may be expected to have a benign and nonprogressive course, and may therefore not receive the attention they need. However, even IgAN patients with a seemingly benign presentation may show a slowly progressive course, develop renal failure and eventually progress to end-stage renal disease (ESRD) after long-term follow-up.[5-8] It would be important to identify these patients at an early stage to allow early treatment directed at slowing or halting progression.

We studied 177 patients with clinically early IgAN, defined by the above criteria. This study was aimed at finding useful markers that allow discrimination between patients with a progressive *vs* a nonprogressive course.

PATIENTS AND METHODS

Patients

In the present study, the patients were selected on the basis of findings from dipstick urinalysis at the periodical physical check-up during a period of ten years from January 1987 to May 1996. In our area, the majority of employees aged 18 to 65 years participate in periodical physical check-ups (usually twice a year). For evaluation of microscopic haematuria and/or proteinuria found by routine examination, patients are referred to the Department of Nephrology at our hospital. Next, patients are screened to rule out known causes of haematuria and/or proteinuria other than glomerular disease, such as urolithiasis and tumours as well as lesions from the lower urinary tract by performing urological investigations.

If the urinary abnormalities persist for more than three months, the patients are advised to undergo a renal biopsy. None of the patients underwent biopsies during bouts of macroscopic haematuria: at least six weeks passed between the last bout of macroscopic haematuria and the renal biopsy. For this study, the patients had to meet the following criteria: 1) the diagnosis of IgAN was established by the presence of immunohistochemical IgA deposition and electron-dense deposits predominantly in the glomerular mesangium. The amount of tissue collected for light microscopy was sufficient for diagnosis in all cases, samples with <10 glomeruli were excluded. Secondary glomerular diseases (systemic lupus erythematosus, diabetes mellitus, Schönlein-Henoch purpura, liver cirrhosis, renal allograft etc.) were excluded; 2) clinical criteria included normal renal function (defined as a glomerular filtration rate ≥90 ml/min/1.73m^2, estimated using the modification of diet in renal disease (MDRD) formula), proteinuria of 0.4 g/d or less, and absence of hypertension; 3) participation in healthcare tests including dipstick urine tests at least twice a year, which could help us to estimate the onset of chronic kidney disease with an error of less than six months. Controls were formed by: 1) subjects with no dipstick abnormalities (normal dipstick group) matched for age and sex; 2) subjects with dipstick abnormalities derived from the same 2023 patients and who had biopsies for the same indication as the IgAN patients, but without abnormalities in their biopsies (normal biopsy group), again matched for age and sex.

Clinical definitions

Prebiopsy duration was defined as the time from the first abnormal urinary finding to renal biopsy. The definition of haematuria was >3 red blood cells per high-power field in the urinary sediment. Proteinuria was defined as total urinary protein excretion >0.15 g/d, using 20% sulphosalicyclic acid. Microalbuminuria was defined as the ratio of urinary albumin concentration to urinary creatinine with levels between 30 to 299 mg/mmol creatinine. We defined the product of urinary protein excretion (g/d) at the time of renal biopsy and prebiopsy duration (months) as UPEI. A patient was regarded as hypertensive if resting systolic blood pressure was >140 mmHg and/or diastolic blood pressure was >90 mmHg. Normal renal function was defined as a GFR ≥90 ml/min/1.73 m^2, estimated using the MDRD formula.

Renal biopsy evaluation

Renal biopsy specimens were divided into three parts for light microscopy, indirect immunofluorescence, and electric microscopy, respectively. To consider the association of IgAN with thin basement membrane nephropathy, the thickness of glomerular basement membrane (GBM) was measured by the orthogonal intercept method.[9] Glomerular lesions included mesangial proliferation, mesangial matrix widening, and glomerular sclerosis. Tubulointerstitial lesions included interstitial cell infiltration, tubular atrophy, and interstitial fibrosis. Besides, pathological evaluation also included hyaline arteriolosclerosis. All lesions were divided into normal, mild, moderate or marked (graded semiquantitatively from 0 to 3, respectively).[7,10,11]

Follow-up assessment

During the follow-up period, the patients visited the clinic every two months. Clinical parameters taken into consideration for each patient were as follows: haematuria, proteinuria, serum creatinine level, and arterial pressure. All parameters were recorded at each clinic visit. The outcome of haematuria was divided into three categories: 1) disappearance; 2) persistent; 3) persistent with development of proteinuria. The outcome of proteinuria was divided into three groups: 1) increased, persistently more than 1 g/d; 2) remission, urinary protein excretion rate decreased to <0.15 g/d; 3) stable. Patients were classified as progressive by the development of renal insufficiency (GFR <60 ml/min/1.73 m^2 in the absence of therapy that reduces GFR). Patients with an urine protein >0.15 g/d and/or hypertension were treated with angiotensin-converting enzyme inhibitors (ACEI) and/or angiotensin receptor blockers (ARB). The indication for prednisone therapy was proteinuria >1 g/d during the follow-up period. The initial dose of oral prednisone was 40 mg/day and reduced to 20 mg/day at the end of the second month, and then slowly tapered over a two-month period. Response to prednisone treatment was defined as follows: 1) responsive: complete remission of urinary abnormalities persisting for at least two months after termination of therapy; 2) dependent: complete remission during prednisone therapy, but recurrence when the dosage was reduced under a critical level or within two months after discontinuing the treatment; and 3) resistant: no remission during ten consecutive weeks of treatment. Remission is defined as a reduction in urine protein <0.15 g/d and reduction of erythrocytes to <3 red blood cells per high-power field.

Statistical analysis

The statistical analysis was run on SPSS 10.0 software for windows. All results are expressed as mean ± SD. Student t-test or the χ^2 test was used in comparisons between individual groups. Logistic regression analysis was used to determine the risk factors of renal progression. Variables included were gender, age, haematuria, proteinuria at biopsy, UPEI, and pathological lesions. A $p<0.05$ was considered to be statistically significant.

RESULTS

Clinical and histological findings at biopsy

In the study period, 2698 patients were referred to the Department of Nephrology for evaluation of urinary abnormalities. Of these, 2602 were screened to rule out urological causes. In 280 patients the urinary abnormalities disappeared. Eventually, 2023 patients underwent a renal biopsy. *Table 1* provides an overview of the renal biopsy diagnosis in relation to the urine abnormalities.

Overall 177 patients with IgAN fulfilled the clinical criteria, and were classified as clinically early IgAN. Clinical characteristics of the patients and the controls are listed in *table 2*. There were no statistical differences. Per definition no patients had hypertension or renal insufficiency. In the early IgAN group, 50 patients (28%) presented with pure haematuria, 28 patients (16%) with isolated proteinuria, whereas concomitant haematuria and proteinuria was the most common manifestation, in 99 patients (56%). Microalbuminuria was more common in IgAN patients.

For the early IgAN group and normal biopsy group, the interval between the first detection of a urinary abnormality and the biopsy was 28 ± 14 (4 to 58) months. In the IgAN patients the thickness of GBM was 359 ± 44 nm for males and 332 ± 39 nm for females. There were no differences in GFR between patients with and without tubular atrophy, and none of the patients had hyaline arteriolosclerosis.

Postbiopsy course

The clinical course during postbiopsy follow-up is listed in *table 3*. The mean follow-up duration from renal biopsy to the last outpatient check-up was 111 ± 43 (109 to 205) months. Out of 149 IgAN patients with haematuria

Table 1. *Renal biopsy diagnosis*

	PH (n)	IP (n)	CHU (n)	Proteinuria (g/d)	Hypertension (n)	GFR (ml/min/1.73 m²)
Immunoglobulin A nephropathy	255	176	318	1.3 ± 0.4	165	87 ± 39
Thin basement membrane nephropathy	218	0	4	0.1 ± 0.06	49	99 ± 41
Membranous nephropathy	3	142	43	1.6 ± 0.5	98	80 ± 37
Non-IgA mesangioproliferative glomerulonephritis	109	19	45	0.8 ± 0.4	36	95 ± 36
Focal segmental glomerular sclerosis	10	53	68	1.9 ± 0.7	77	74 ± 35
Systemic lupus erythematosus	5	22	70	1.2 ± 0.4	18	86 ± 36
Diabetic nephropathy	0	74	5	1.7 ± 0.8	72	79 ± 37
Hypertensive nephropathy	1	51	3	0.9 ± 0.4	65	82 ± 38
Schönlein-Henoch purpura	13	9	33	1.0 ± 0.5	16	90 ± 38
Focal segmental proliferative glomerulonephritis	8	13	15	0.7 ± 0.3	6	89 ± 40
Minimal change disease	0	30	4	1.2 ± 0.6	1	93 ± 37
Sclerosing glomerulonephritis	0	12	8	2.5 ± 0.9	18	42 ± 20
Membranoproliferative glomerulonephritis	0	7	11	2.1 ± 0.8	15	64 ± 31
Normal biopsy	88	25	30	0.1 ± 0.05	2	98 ± 39

PH = pure haematuria; IP = isolated proteinuria; CHU = concomitant haematuria and proteinuria; GFR = glomerular filtration rate; ± values = ± SD.

Table 2. *Clinical data at the time of renal biopsy*

	Early IgAN	Normal biopsy	Normal dipstick
Patients (n)	177	135	120
Female /male (n)	69/108	40/95	37/83
Age (years)	38 ± 16	38 ± 15	37 ± 16
Prebiopsy duration (months)	27 ± 15	28 ± 14	
Presentation:			
• Pure haematuria	50	35	-
• Isolated proteinuria	28	23	-
• Combined haematuria and proteinuria	99	77	-
Systolic blood pressure (mmHg)	124 ± 11	123 ± 10	127 ± 12
Diastolic blood pressure (mmHg)	73 ± 10	74 ± 11	72 ± 10
Urinary protein excretion (g/d)	0.24 ± 0.11	0.23 ± 0.09	0.08 ± 0.05
Microalbuminuria (n)	133	76	46
Normoalbuminuria (n)	44	59	74
Glomerular filtration rate (ml/min/1.73 m²)	100 ± 23	102 ± 22	102 ± 21

± Values = ± SD.

Table 3. *Clinical data at the end of follow-up*

	Early IgAN	Normal biopsy	Normal dipstick
Patients (n)	177	135	120
Haematuria:			
• Disappearance	18 (10%)	67 (50%)	0 (0%)
• Persistent	135 (76%)	41 (38%)	5 (4%)
Proteinuria:			
• Remission	10 (6%)	90 (67%)	0 (0%)
• Stable	50 (28%)	14 (10%)	0 (0%)
• Increased	79 (46%)	3 (3%)	2 (2%)
Hypertension	68 (38%)	11 (8%)	8 (7%)
Renal insufficiency	43 (24%)	0 (0%)	0 (0%)

at presentation, the haematuria disappeared in 18 and persisted in 131 patients. In addition, four patients with isolated proteinuria developed haematuria. Twelve patients with IgAN and isolated haematuria developed proteinuria, and proteinuria increased to values >1 g/d in 14 out of 28 patients with isolated proteinuria and in 53 of 99 patients with combined haematuria and proteinuria. Proteinuria disappeared in only two out of 28 and eight out of 99 patients respectively. From *table 3* it is evident that urine abnormalities disappeared in more than half of the patients with a normal biopsy.

Patients with IgAN developed hypertension more frequently. Renal insufficiency was only observed in patients with IgAN and developed in 43 (24%) of the patients. No patient thus far has reached ESRD. The initial presentation of patients with renal insufficiency was pure haematuria in eight, concomitant haematuria and proteinuria in 27, and isolated proteinuria in eight patients. All patients with renal insufficiency had proteinuria; in 39 the urine protein was >1 g/d.

During the follow-up period, 138 patients with urine protein >0.15 g/d and/or hypertension were treated with ACEI and/or ARB. Of the 138 patients, 130 patients were in the early IgAN group, five patients were in the normal biopsy group, and three patients were in the normal dipstick group.

During the course of the follow-up, 79 early IgAN patients with increasing proteinuria (proteinuria increased to more than 1 g/d) were advised to start treatment with prednisone, and 52 of the 79 patients agreed to receive immunosuppressive therapy. Of the 52 patients, four complained of some unbearable side effects of the medication such as gastric discomfort, two patients had severe complications such as serious infections. Finally, seven patients were forced to abandon immunosuppressive therapy, and the 45 patients left were completely followed up. Regarding the response to prednisone therapy, 30 patients responded, nine patients were prednisone-dependent, and six patients were resistant.

Risk factors for renal progression

As indicated, 43 patients with early IgAN developed renal insufficiency and were considered progressive. Regression analysis was performed to establish useful prognostic indicators for clinically early IgAN patients. All variables including gender, age, haematuria, proteinuria at biopsy, UPEI, and pathological lesions were analysed separately. The renal outcome was not correlated with gender, age, proteinuria at biopsy, and glomerular lesions; whereas poor outcome was correlated with haematuria, UPEI, and tubulointerstitial lesions (*table 3*). The UPEI in the progressive group was significantly higher than that in the nonprogressive group (25 ± 14 *vs* 13 ± 10 g/d·m, p<0.01).

DISCUSSION

In mass screening of healthy adults, the positive rate of urinary abnormalities is extremely high. For haematuria, 1.2 to 21.1% of the subjects were positive, and 0.4 to 4.9% of the subjects were positive for proteinuria using dipstick analysis of urine.[12-14] In our area, 8.5% of the subjects were positive for haematuria and 3.1% were positive for proteinuria. Our policy has been to perform a renal biopsy in a patient with persistent urinary abnormalities for more than three months after exclusion of nonglomerular diseases. Most of these patients in our cohort would not have undergone renal biopsy in many parts of the world. However, our patients fulfil the definition of chronic kidney disease (CKD) stage I, since the duration of urinary abnormalities was more than three months. Primary chronic glomerulonephritis is the most common cause of primary renal disease worldwide. Ultimately up to 40% of patients may progress to chronic renal failure, and spontaneous remission is distinctly uncommon.[14] The clinical onset of primary chronic glomerulonephritis can be silent, and is often manifested by asymptomatic urinary abnormalities. However, even patients with

Table 4. *Risk factors for renal progression*

Variables	Odds ratio	P value
Gender	0.616	0.897
Age	1.387	0.742
Haematuria	2.734	0.041
Proteinuria at biopsy	2.035	0.356
Urinary protein excretion index	3.127	0.038
Mesangial proliferation	1.495	0.656
Mesangial matrix widening	0.839	0.762
Glomerular sclerosis	1.996	0.352
Interstitial cell infiltration	5.317	0.014
Tubular atrophy	4.235	0.028
Interstitial fibrosis	2.096	0.091

mild renal symptoms at the onset may carry a risk for severe long-term complications.[7,15] Also, there are often discrepancies between the clinical symptoms and the severity of histological lesions.[4,16] Performing a renal biopsy until more overt signs of progressive nephropathy occur may cause inappropriate delay of management.

The natural history of patients with IgAN is not completely understood, although it is useful to establish a profile of clinicopathological features in order to determine whether a patient is at high risk for renal insufficiency. In the present study, the patients periodically had a urinary examination which enabled investigation of the natural history with an error of less than six months. So, we had a good chance to observe the natural history of the patients with clinically early IgAN. In our study the interval between the detection of urine abnormalities and renal biopsy was 28 ± 14 months. The reason is that either these patients did not seek medical attention in time or they hesitated to undergo renal biopsy. On the other hand, we wanted to follow up the urinary abnormalities for some time to evaluate if the urinary abnormalities were transient or chronic.

Spontaneous remission and permanent disappearance of all abnormal urinary findings are distinctly uncommon in IgAN patients. Patients with seemingly benign presentation can become azotaemic or even develop end-stage renal insufficiency after long-term follow-up.[3,17] None of our patients had poor prognostic factors such as heavy proteinuria, hypertension, and renal insufficiency at presentation due to the inclusion criteria of this study. However, during the follow-up period, we did find that proteinuria increased and hypertension developed in 46 and 38% of the patients, and 24% of the patients suffered from a certain degree of renal function deterioration, as observed in several previous studies.[7,18] Proteinuria and hypertension are considered to be two of the most important factors responsible for accelerating the progression of renal lesions.[19] Thus, life-long follow-up with regular monitoring of blood pressure, proteinuria and renal function is recommended for the patients with clinically early IgAN.

With respect to the association between the number of urinary erythrocytes and renal outcome, there is no firm conclusion. Our results suggested that haematuria played an unfavourable role in the course of IgAN. The rising level of urinary erythrocytes might indicate a high degree of glomerular inflammation in the early course of renal disease. Association of haematuria with renal function progression was only observed in patients with initially normal renal function.[16] It seems that the prognostic value of haematuria is greater in the early stage of IgAN. Of note, we observed that four patients with initially an isolated proteinuria developed haematuria, and finally three of them were classified into the progressive group.

It has been well documented that high-grade proteinuria is a risk factor for poor outcomes.[20,21] However, in the present study, the level of proteinuria at the time of renal biopsy was no more than 0.4 g/d, so it had limited value in predicting probability of developing renal progression. On the other hand, we found that UPEI (defined as the product of urinary protein excretion at the time of renal biopsy and prebiopsy duration) may be a valuable marker for predicting renal progression. Considering that proteinuria contributes to renal damage, we speculated that this result might depend on the amount of proteinuria from the onset of the disease to the time of renal biopsy. Moreover, it has been reported that patients with progressive proteinuria during the course were more liable to have renal function deterioration than those with proteinuria at the beginning.[14,22,23] As mentioned above, in our research, we could identify the time of onset of IgAN with an error of less than six months. Hence, the accumulation of proteinuria could be an important prognostic factor for renal progression in IgAN, and we are able to approximately estimate it by UPEI.

In the present study, the interstitial lesions, mainly interstitial cell infiltration and tubular atrophy, were better prognostic indicators for renal outcome as compared with the glomerular lesions. Our data are in agreement with those of other authors.[7,19,24,25] They advocate tubulointerstitial changes as the most reliable predictor of chronic and irreversible renal damage in chronic glomerular diseases, as were some other parameters such as proteinuria. In this regard, it has been well documented that tubular lesions reflect the ability of interstitial processes to damage normal glomeruli and to contribute to a greater nephron loss.[26]

The prevalence of IgAN differs greatly between geographic locations, being 29.2% of the biopsied population in Asia, 12% in Australia, 10.7% in Europe and 5% in North America, so IgAN is more prevalent in Asian countries including China. Moreover, unlike in developed countries, primary chronic glomerulonephritis other than hypertensive nephropathy and diabetic nephropathy is the leading cause of ESRD in developing countries. Therefore, it is uncertain how applicable the results in Chinese subjects are for people from other regions in the world.

CONCLUSION

Our observations suggest that renal progression may occur in a considerable number of patients with clinically early IgAN. We further highlight that haematuria, UPEI or tubulointerstitial lesions might be useful markers to identify high-risk patients with renal progression. It may add extra information to identify people at a high risk for developing renal insufficiency, who may benefit from preventive strategies, early therapy and closer follow-up.

NOTE

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