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Original Article

Course of IgA Nephropathy: follow-up of 23 years

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Abstract

Background. IgA nephropathy (IgAN) accounts for 11.8% of primary glomerulonephritides (GN) in R. Macedonia. IgAN presents with variable onset and shows unpredictable outcomes.
Methods. To evaluate the association of risk factors with the progression of IgAN to renal failure we examined eighty patients diagnosed by renal biopsy (RB). We used H. S. Lee's grading system to score the severity of histological involvement. Baseline clinical and demographic data were reviewed. Patients were followed-up from 6 to 276 months. Male: female ratio was 58:22; the mean age was 36.65±8.83 years. The date when patients underwent their first haemodialysis or their last visit was defined as an end-point. Independent samples *t*-tests or one-way analysis of variance (ANOVA) were used to compare the differences in means between groups. Kaplan-Meier survival curves and Cox regression models were used to analyze the time course from renal biopsy to end points.
Results. The largest subclasses were grade I and II, with 31 patients each. All patients with grade IV and V (after 6-48 months), five patients grade I (after 60-144 months), four patients grade II (after 48-84 months), and 7 patients from grade III (after 24-108 months) entered ESRD. Macrohematuria had 32; microhematuria had 48 patients. Mean proteinuria was 1.68±0.99 g/day and the mean serum creatinine was 148.02±68.76 μmol/l. By multivariate analysis using the Cox regression model, grades, renal insufficiency and significant proteinuria were independent prognostic factors for progressive renal disease. At the end of follow-up, grades were significantly related to serum creatinine, proteinuria, hypertension and progressive renal disease.
Conclusions. Renal biopsy remains the most powerful predictor for renal outcome. Determining the patient who might develop ESRF over time based on clinical and histological renal findings remains a challenge.

Keywords: IgA nephropathy, follow-up, renal prognosis, histological grading

Introduction

Idiopathic IgA nephropathy (IgAN), the most prevalent primary glomerulonephritis (GN) in the world, accounts for 11.8% of all forms of primary GN in Macedonia [1,2]. The differences between countries are due to the length of the follow-up period, the geographic variability and differences in disease prevalence (Italy 21%, Nederland 13%, Spain 15%, Check Republic 21%, China 31%), different histological criteria of classification, different indications of biopsy. It is possible that the potential differences in the progression of the disease are due to therapy and what is the means of "natural course". All patients in the present study were not on treatments modulating immune and inflammatory injury.
IgAN is an immune-complex-mediated GN first described by Berger and Hinglais in 1968, morphologically characterized by IgA deposition in the glomerular mesangium [3]. It occurs predominantly in young people and presents with variable onset and shows different outcomes [4]. Initially it was believed to be a benign and non-progressive disease but now days IgAN is the second or third most common primary GN to terminate in ESRD in many of the world's registries. In Europe as a whole, approximately 24% of histological examined patients have IgAN as cause of ESRD [5]. Complete remission is also reported in 5 to 30% of cases. [6]. The aim of the present study was to examine the associations of the previously identified factors (demographic, clinical, laboratory, and histological parameters) at the time of renal biopsy with the progression to renal failure in our population.

Patients and methods

Eighty Macedonian Caucasians with biopsy-proven IgAN were enrolled in retrospective follow-up study. Patients aged older than 15 years at presentation were considered adults. Patients who suffered from systemic diseases (Systemic lupus erithematodes, Henoch-Schönlein purpura, Diabetes mellitus, collagen disease, and chronic liver disease) or had previous treatment with steroids or immunosuppressants were excluded. The parameters were evaluated at the time of renal biopsy (the initial values), and at the last outpatient check-up. Baseline clinical and demographic data were taken into consideration for each patient: age, sex, microscopic or macroscopic hematuria, 24-h proteinuria, systolic and diastolic blood pressure (sBP, dBP) and renal function (serum creatinine concentration, sCr). Patients with hypertension (BP>130/90 mmHg) ex novo at first observation and those on hypertensive pharmacological treatment were considered as hypertensive. Patients were followed up for 6 to 276 months. An end-point was defined as the date when patients underwent their first haemodialysis or their last visit of follow-up.
Percutaneous renal biopsies were taken using a TruCut needle; two specimens were taken for each renal biopsy, for light microscopy (minimum of 8 glomeruli) and for immunofluorescence study. The indications for renal biopsy

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were persistent microscopic hematuria, proteinuria >0.5g/day and unexplained renal impairment. All specimens were reviewed by a single pathologist unaware of the patients' clinical condition. IgAN was diagnosed by the typical appearance of mesangial proliferative GN on light microscopy with predominant mesangial IgA deposition with C3 deposition on immunofluorescence microscopy.

Meadow [7] and H. S. Lee's [8] grading system were used for scoring the severity of histological involvement. Grade I: normal glomeruli without crescents/segmental lesions. Grade II: <50% glomeruli showing mesangial cell proliferation, with or without crescents/segmental lesions in <15% glomeruli; a) without/minimal interstitial fibrosis and/or tubular atrophy, and b) with mote than minimal interstitial fibrosis and/or tubular atrophy as well as arteriolar lesions. Grade III: >50% glomeruli showing proliferation, with crescents/segmental lesions in <50% glomeruli; a) associated with tubulointerstitial lesions of IIa, and b) associated with tubulointerstitial lesions of IIb. Grade IV: >50% glomeruli showing proliferation, with crescents/segmental lesions/global sclerosis in >50-75% glomeruli, with IIIb. Grade V: >50% glomeruli showing proliferation, with crescents/segmental lesions/global sclerosis in >75% glomeruli, with IIIb.

Data analysis

All numerical data are expressed as mean±SD. The differences in means between groups were compared by t-test and one-way analysis of variance (ANOVA). Post hoc analysis was performed by the Bonferroni's method. The effect of prognostic factors was studied as stratifying variable with univariate analysis by log-rank test. Multivariate survival analysis was performing using the Cox proportional hazard regression method to identify independent factors. Renal survival was estimated by the Kaplan-Meier method. A value of $P<0.05$ was considered to indicate statistical significance.

Results

The average age of 80 patients at biopsy was 36.65±8.83 years (range 15-67). There were 58 males and 22 females [male: female ratio, 58:22]. 90% of all cases presented under 45 years of age; all patients with grade IV and V were above 40 years of age. The mean proteinuria was 1.68±0.99 g/day. 54% of patients had significant proteinuria of >1g/day; 21% showed nephritic range proteinuria of ≥3.5 g/day. The mean serum creatinine was 148.02±68.76 μmol/l. Renal insuffici-ency (sCr level of 132 μmol/l) was observed in 14%. Arterial hypertension was found in 35%. 60% (48 patients) had microscopic and 40% (32 patients) had macroscopic hematuria. The clinical features at the time of biopsy are shown in Table 1.

Table 1. Clinical data in relation to glomerular grades at the time of biopsy in patients with IgA nephropathy

	Glomerular grades					F	P†
	I	II	III	IV	V		
n (%)	31 (38.7)	31 (38.7)	12 (15)	3 (3.7)	3 (3.7)		
Age (years)	26±10	30±11	31±12	44±0	47±8	4.4	< 0.003*
Sex (M:F)	25:6	24:7	6:6	2:1	1:2		NS#
sCr (μmol/l)	68±19	85±31	121±78	177±84	228±118	13.3	< 0.001*
Proteinuria (g/24h)	1.1±1	1.6±1.3	1.5±1.3	2.5±2.3	2.3±1	1.8	NS*
Microscopic Hematuria (n [%])	19 (61)	19 (61)	6 (50)	1 (33)	3 (100)		NS#
Macroscopic Hematuria (n [%])	12 (39)	12 (39)	6 (50)	2 (67)	0 (0)		NS#
Systolic BP	129±17	130±19	145±19	148±19	177±12	6.6	< 0.001*
Diastolic BP	85±10	82±18	93±15	97±15	103±6	2.7	< 0.05*

Values represent mean ± SD. NS not significant. BP, blood pressure
†Data are compared with *ANOVA or #chi square test

Younger age was significantly related to lower histological grades ($P<0.003$). The frequency of arterial hypertension (systolic BP, $P<0.001$; diastolic BP, $P<0.05$) and sCr levels increased as the histological grade became higher ($P<0.001$). The distribution in glomerular grades was: grade I, 38.75%; grade II, 38.75%; grade III, 15%; grade IV, 3.75%; and grade V, 3.75%. No significant difference with respect to sex, 24-h proteinuria and frequency of microscopic/macroscopic hematuria was observed between different grades.

The followed-up period was from 6 months to 23 years (276 months). 28.75% patients progressed to ESRD and continued on long-term haemodialysis; all patients with grade IV (100%, up to 4 years) and grade V (100%, after 6 months to 2 years), five patients grade I (16.13%, from 5 to 12 years), five patients grade II (16.13%, after 4 to 7 years), and seven patients grade III (58.33%, after 2 to 9 years). One patient died, due to carcinoma (5 years from the diagnosis). At the end of follow-up, hypertension was observed in 56.25%, significant proteinuria (>1g/day) in 62.5% and renal insufficiency (sCr >132 μmol/l) in 33.75% of the patients. Mean values of sCr and the frequency of hypertension and progressive renal disease at the end of follow-up were significantly increased in accordance with increased glomerular grades ($P<0.001$, $P<0.003$) (Table 2).

Table 2. Clinical data in relation to glomerular grades at the end of follow-up

	Glomerular grades					F	P†
	I (n=31)	II (n=31)	III (n=12)	IV (n=3)	V (n=3)		
sCr (μmol/l)	154±212	208±260	492±388	859±112	714±42	10.2	< 0.001*
Proteinuria (g/24h)	1.1±0.8	1.5±1	1.9±1.3	1.7±0.9	2±1.6		NS*
Systolic BP	132±16	142±21	161±17	163±15	182±8	9.8	< 0.001*
Diastolic BP	87±9	90±13	104±11	107±12	115±18	9.6	< 0.001*
Long-term HD (n %)	5 (16)	5 (16)	7 (58)	3 (100)	3 (100)		< 0.003#

Values represent mean ± SD. NS not significant. BP, blood pressure. HD, hemodialysis
†Data are compared with *ANOVA or #chi square test

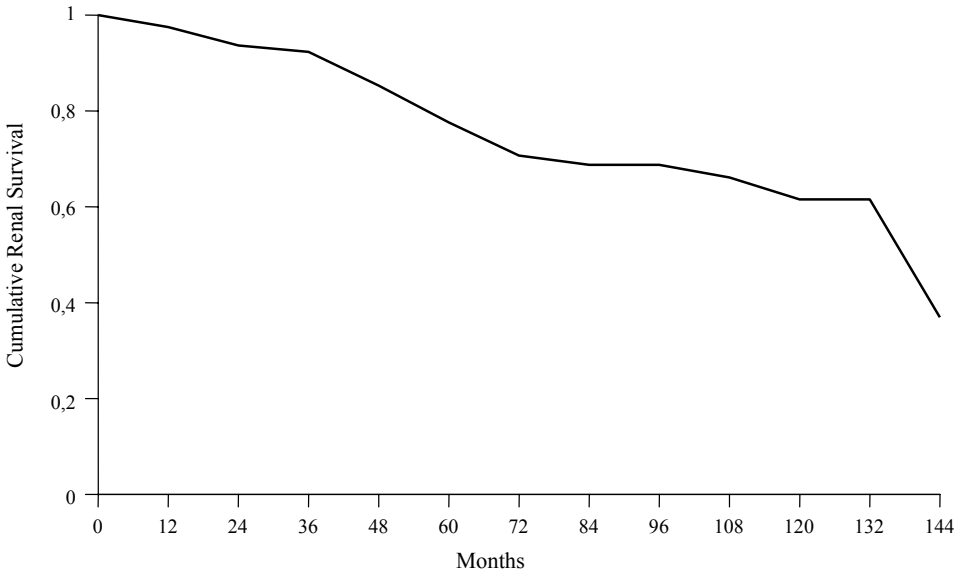

Fig. 1. The Kaplan-Meier renal survival curve of 80 patients with IgA nephropathy.

The renal survival was 97.5% at 1 year, 77.5% at 5 years and 61.5% at 10 years. The Kaplan-Meier survival curve is shown in Figure 1.

With multivariate analysis, renal impairment at presentation, proteinuria >1g/day and high histological grading were associated with worse renal survival (data not showen). Patients with serum creatinine >132 μmol/l at presentation ended with renal dead in the first 60 months. According to multivariate analysis, using the Cox proportional hazard regression model, systolic (P<0.01) and diastolic blood pressure (P<0.05), and significant proteinuria >1g/day (P<0.05) were high independent prognostic factors for (renal) survival (Table 3). There was no significant effect of gender on renal outcome demonstrated.

Table 3. Significance of clinicopathological variables as predictors of renal survival using the proportional hazard model

Variables	*P*-value	Standardized coefficients Beta	*t*
Systolic blood pressure	0.001	0.536	3.589
Diastolic blood pressure	0.018	0.315	2.430
Proteinuria >1g/day	0.022	0.202	2.350

Discussion

IgA nephropathy is a very frequent glomerular disease with slow rate of progression and is necessary to study patients for prolonged periods of time. The follow-up period of our patients was long; the longest recorded period was 23 years (276 months). The variable prognosis of patients may depend upon the different phases of a disease and time of renal biopsy, true genetic susceptibility differences and geographic differences in urinalysis screening practices or differences in indications for renal biopsy. The choice of moment for performing the renal biopsy strongly influences what we appreciate as the natural history of the renal disease. Renal survival after 10 years was 61.5%, similar to the reported Figures from Europe, Australia and North America [9,10]. Extensive studies have resulted in a partial consensus that arterial hypertension [6,11], proteinuria [12], hematuria [6,13] and impaired renal function at presentation [9,14,15] are the risk factors of progression. On the other hand, a large number of reports have favored histopathologic changes, glomerular sclerosis [14], tubulointerstitial lesions [6,16,17], mesangial cell proliferation [17], and/or crescents [6,8] as (negative) prognostic factors. In our population, renal impairment, arterial hypertension, proteinuria >1g/day and histological grading at presentation were the major predictors of renal survival. The prevalence of patients presenting with arterial hypertension and significant proteinuria increased during the follow-up. The prevalence of decreased renal function, present in 14% of the patients at the onset of the disease, had risen to 33.75% by the end of follow-up. These data confirm that the prognosis of IgAN is not as good as was initially described. The present study confirms that IgAN occurs at a young age, predominately in males (72.5%); moreover microscopic hematuria is the presenting symptom in 60% of cases. These results are similar to other reports [6]. In the present study, higher glomerular grades were associated with arterial hypertension, higher sCr levels and older age at the time of biopsy. These findings are in agreement with previous reports on IgA [6,10,11]. We do not exclude the possibility that age affects the prognosis in IgAN. The presence of renal failure at the time of diagnosis has been reported as an unfavorable prognostic factor. D'Amico *et al*. reported that there is a 'point of no-return', when the patients gets sCr above 3 mg/dl [9]. Over this limit the functional decline presents a rapid acceleration. A more recent Komatsu and collaborative German study have confirmed these findings [15]. Once renal failure occurs, the evolution to ESRF is practically predictable. We found a little percentage of patients with advanced phases of IgAN and increased Cr level at the time of biopsy. The possible explanation for this is the patients' early referral to the nephrologists. In general all the studies consider

proteinuria values >1g/day as the most significant risk factor for progression [12]. Patients with nephrotic-range proteinuria >3.5g/day were found to have a yearly loss of renal function of 9 ml/year. IgA nephropathy is characterized by microscopic and macroscopic hematuria but results from the authors regarding the recurrent bouts of macroscopic hematuria as predictor are conflict [6].

We observed that higher glomerular grades were related to the occurrence of hypertension and higher levels of sCr at the end of follow-up. Grade IV and V; in particular, were most significantly associated with loss of renal function and progression. The Lee's classification system estimates tubulointerstitial damage with increasing severity in two grades (IV and V). Tubulointerstitial lesions are considered as indicator of chronic and irreversible renal damage, unlike crescents or proliferative lesions that may regress. Tubulointerstitial injury strongly and directly correlates with renal outcome in IgAN, similar to most other glomerular diseases [6,16,17]. The strong independent predictors of progression are the severity of glomerular sclerosis and interstitial fibrosis.

Adverse clinical features at presentation include hypertension, proteinuria, and renal failure. But, none of the features that mark a poor prognosis are specific to IgAN [18]. A better understanding of the pathogenesis of IgAN may contribute in development more specific therapeutical approaches [19,20]. Recent years there are a lot of studies about therapeutic intervention in IgAN. Because the treatment remains a dilemma (who is high-risk patient, who should be treated, what is the best therapy for one patient) we believe that the renal biopsy in patients with microscopic haematuria and proteinuria is mandatory to prevent renal failure as the main focus of the therapy.

Conclusion

In conclusion, our long-term follow up confirms that that IgAN occurs at a young age, predominately in males and microscopic hematuria is the presenting symptom. Histological features at renal biopsy with higher glomerular grades are associated with arterial hypertension, higher sCr levels and older age at the time of biopsy. Increasing evidence now confirm that the prognosis of IgAN is not as good as was initially believed.

Conflict of interest statement. None declared.

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