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Prognostic Factors and Renal Survival Rates in IgA Nephropathy

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A retrospective study of 223 patients with IgA nephropathy (IgAN) was performed to clarify the prognostic factors and the renal survival rates of the disease. One hundred twenty-two patients were followed-up for more than 6 months after their renal biopsy (mean follow-up duration: 43.0 months), and 20 of them (16.4%) had progressed to end-stage renal disease (ESRD). Using univariate analysis, 8 risk factors (2 clinical and 6 histopathological findings) for developing ESRD were identified: renal insufficiency at initial presentation (serum creatinine≥1.5mg/dl); heavy proteinuria (≥3.5gm/day); moderate to severe histopathologic findings such as class IV/V lesions by W.H.O. classification, mesangial hypercellularity, glomerular sclerosis, intersfitial infiltration, interstitial fibrosis, and tubular atrophy. In multivariate regression analysis, class IV/V lesions and renal insufficiency at initial presentation were the independent prognostic factors of IgAN. The renal survival rates were 100% at 1 year, 97.0% at 3 years, and 78.9% at 5 years. In conclusion, it seems that about 20% of IgAN patients have a risk to progress to ESRD within 5 years, and a careful follow-up is recommended especially in patients who have either renal insufficiency at the time of presentation or severe renal pathology (class IV/V lesions).

Key Words: IgA nephropathy, Prognostic factor, Renal survival rate

Idiopathic IgA nephropathy (IgAN) is the most common type of primary glomerulonephritis in human (Clarkson *et al.* 1977; Sinniah *et al.* 1981; D'Amico *et al.* 1985; Woo *et al.* 1986; Lee *et al.* 1987; Choi *et al.* 1991). It was first described by Berger (1969) and initially considered as a benign disease, but the natural history of this disease has changed. Recent studies have shown that IgAN progresses to ESRD in 5% to 23% of cases (Berger *et al.* 1975; D'Amico *et al.* 1981; Kobayashi *et al.* 1983; Beukhof *et al.* 1986; Woo *et al.* 1986; Kusumoto *et al.* 1987; Alamartine *et al.* 1991), and the renal survival rates of IgAN vary from 76% to 94% at 10 years, and 47% to 83% at 20 years (Droz 1976; Rodicio 1984; D'Amico *et al.* 1985; Beukhof *et al.* 1986; Kusumoto *et al.* 1987; Alamartine *et al.* 1991).

It is very important to determine the prognostic factors for IgAN, because its natural course is not modified according to the treatment modalities, and the individual patient progresses to ESRD at various times after his diagnosis. Numerous recent reports revealed some clinical signs, laboratory findings, and histopathologic features could predict the prognosis of IgAN (Hood *et al.* 1981; Bennett and Kincaid-Smith 1983; Katz *et al.* 1983; Lévy *et al.* 1985; Praga *et al.* 1985; Beukhof *et al.* 1986; D'Amico *et al.* 1986; Woo *et al.* 1986; Alamartine *et al.* 1991), but there have been only a few reports for the prognosis of this

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disease in Korea (Lee *et al.* 1987).

Therefore, we evaluated not only the prognosis of IgAN in regard to the clinical, laboratory, and histopathologic findings of the patients but also the renal survival rates based on the initial renal function.

PATIENTS AND METHODS

Patients

IgAN was diagnosed in 223 patients at Yonsei University College of Medicine from January, 1980 to June, 1993. The diagnosis for IgAN was confirmed through renal biopsy specimen which demonstrated predominant mesangial IgA deposits on immunofluorescent microscopy. The patients were excluded if there was clinical or serological evidence of systemic lupus erythematosus, Henoch-Schönlein purpura, chronic liver disease, or ankylosing spondylitis. The clinical features of the patients were obtained through careful review of their medical records.

One hundred twenty-two patients were followed-up for more than 6 months after their renal biopsy, 119 for more than 1 year, 76 for more than 3 years, and 41 for more than 5 years.

Methods

Clinical and laboratory findings: For all patients, history taking along with physical examinations including blood pressure measurements were done. Serum blood urea nitrogen and creatinine were measured using an SMA autoanalyzer, and twenty-four hour urinary protein excretion was measured by the Biuret method. Serum IgA was determined by the single radial immunodiffusion technique using monospecific antisera (Behring Institute) until June, 1991, and by the nephelometric method using Beckman reagents thereafter.

Histopathologic findings: Renal biopsy specimens were routinely divided into 3 pieces for light, immunofluorescent, and electron microscopy. For the light microscopical examination, the specimen was fixed in 10% neutral formalin, embedded either in paraffin or plastic, serially cut at 4~5 μm or 1 μm thickness, and stained with hematoxylin-eosin, periodic acid-Schiff, Masson's trichrome, and periodic acid-Schiff methenamine silver stains.

For the immunofluorescent microscopical examination, a portion of the fresh renal tissue was frozen, exposed to FITC-conjugated antihuman -IgG, -IgA, -IgM, -C3, -C4, -C1q, and -fibrinogen (Meloy Inc.), and examined with a Leitz dialoux immunofluorescent microscope. The intensity of mesangial immune deposits was divided into four categories: trace (±), mild (+), moderate (++), and severe (+++).

We reviewed the light microscopical findings of the biopsy specimen in 193 patients. The histopathologic lesions of the glomeruli were subdivided into 5 classes according to the criteria of W.H.O. (W.H.O. classification and atlas of glomerular diseases 1982). In addition, seven specific histopathologic changes such as mesangial hypercellularity, cellular crescents, fibrous crescents, glomerular sclerosis (segmental or global), interstitial infiltration, interstitial fibrosis, and tubular atrophy were evaluated according to semi-quantitive methods as absent, mild, moderate, and severe.

Statistical analysis: Patients who were followed up for more than 6 months were divided into two groups according to the last follow-up clinical and laboratory findings. If the patients had progressed to end-stage renal failure, they were grouped into the ESRD group, and if not, into the non-ESRD group. The ESRD group was consisted of 20 patients, and the non-ESRD group of 102. We compared these two groups in terms of sex; of age at the time of renal biopsy; of the presence of hypertension (BP>150/95 mmHg), gross hematuria, heavy proteinuria (≥3.5 gm/day), and renal insufficiency at the time of presentation (serum creatinine≥1.5 mg/dl); of serum IgA level; and of histopathologic changes on biopsy using the chi-square test or the unpaired Student's t-test analysis. With the results of univariate analysis, the adverse conditions of patients with IgAN were tested using multivariate regression analysis with stepwise method.

The renal survival rates after each biopsy were calculated with the life table method (Culter and Ederer 1958), and they were com-

pared according to the initial serum creatinine level. Data was expressed as mean±S.D., and $p<0.05$ was considered statistically significant.

RESULTS

Clinical and laboratory findings

Table 1 shows the clinical and laboratory features of the 223 patients. The mean age was 26.0±11.6 years, ranging from 6 to 68 years. The sex ratio (M : F) was 1.48 : 1. Hypertension (BP>150/95 mmHg) was observed in 24 patients (10.8%), and 25 patients (11.2 %) had initial serum creatinine level higher than 1.5 mg/dl. One hundred seventy-nine patients (80.3%) had hematuria, including gross hematuria in 75 (33.6%), and microscopic hematuria in 104 (46.6 %). Heavy proteinuria (≥3.5 gm/day) was present in 27 patients (12.1 %) and serum IgA was found to be elevated (≥350 mg/dl) in 57 patients (33.5%).

Table 1. Clinical and laboratory findings of patients with IgAN at initial presentation

	No. of patients (%)
Age (years)	26.0±11.6*
Sex ratio (M:F)	133 : 90
Hypertension (B.P.>150/95 mmHg)	24(10.8)
Renal insufficiency (serum Cr. ≥1.5 mg/dl)	25(11.2)
Hematuria	179(80.3)
Gross hematuria	75(33.6)
Microscopic hematuria	104(46.6)
Proteinuria (gm/day)	163(73.1)
Heavy proteinuria (≥3.5)	27(73.1)
Moderate proteinuria (1.0~3.5)	77(34.5)
Mild proteinuria (0.2~1.0)	59(26.5)
High serum IgA (≥350 mg/dl)	57/170(33.5)
Total	223(100.0)

*Mean±S.D.

Histopathologic findings

Concerning the severity of glomerular lesions, class II lesions were most frequent, as 78 patients (40.4 %), class III lesions in 76 (39.4%), class IV lesions in 23 (11.9%), class V lesions in 9 (4.7%), and class I lesions in 7 patients (3.6%), in order (Table 2).

Table 2. Histopathologic findings of patients with IgAN by W.H.O. classification

	No. of patients(%)
Class I	7(3.6)
II	78(40.0)
III	76(39.4)
IV	23(11.9)
V	9(4.7)
Total	193(100.0)

Table 3. Univariate analysis of clinical and laboratory findings

Clinical and laboratory findings	All (N=122)	Non-ESRD (N=102)	ESRD (N=20)	χ^2 or t	p
Age (years)	27.9±11.4*	28.2±12.2	26.6± 6.0	0.59	NS**
Male	75(61.4)#	60(58.8)	15(75.0)	1.23	NS
Hypertension	18(14.8)	14(13.7)	4(20.0)	0.14	NS
Renal insufficiency	19(15.6)	8(7.8)	11(55.0)	24.81	<0.001
Gross hematuria	42(34.4)	38(37.3)	4(20.0)	1.51	NS
Heavy proteinuria	17(13.9)	9(8.8)	8(40.0)	11.08	<0.001
High serum IgA	33/94(35.1)	27/77(35.1)	6/17(35.3)	<0.01	NS

* Mean±S.D.
** Not significant
# Numbers in parentheses are percentages

Table 4. Univariate analysis of histopathologic findings

Histopathologic findings	All (N=117)	Non-ESRD (N=97)	ESRS (N=20)	χ^2	p
Class IV/V by W.H.O.	25(21.4)*	11(11.3)	14(70.0)	30.56	<0.001
Specific histopathologic changes (moderate to severe)					
Hypercellularity	52(44.4)	38(39.2)	14(70.0)	5.19	<0.05
Cellular crescents	4(3.4)	2(2.1)	2(10.0)	1.21	NS*
Fibrous crescents	3(2.6)	1(1.0)	2(10.0)	2.35	NS
Glomerular sclerosis	37(31.6)	21(21.6)	16(80.0)	23.48	<0.001
Interstitial infiltration	29(24.8)	16(16.5)	13(65.5)	18.40	<0.001
Interstitial fibrosis	30(25.6)	18(18.6)	12(60.0)	12.84	<0.001
Tubular atrophy	29(24.8)	16(16.4)	13(65.0)	18.40	<0.001

* Numbers in parentheses are percentages
* Not significant

Table 5. Multivariate analysis of risk factors with stepwise method

Step	Risk factors	β	SE	β/SE	p
1	Class IV/V lesions by W.H.O.	+0.495	0.072	+6.875	<0.0001
2	Renal insufficieny	+0.321	0.082	+3.915	0.0002

Note: For each risk factor, it quantified its effect on the hazard (β regression coefficient with its standard error, SE), its relative weight compared with other risk factors (β/SE).

Univariate analysis of risk factors

Clinical and laboratory findings: The clinical and laboratory findings from 122 patients were compared between the ESRD and the non-ESRD group in Table 3. The presence of renal insufficiency at the time of presentation (serum creatinine $\geq$ 1.5 mg/dl) ($\chi^2 = 24.81$, $p < 0.001$) and heavy proteinuria ($\geq$3.5 gm/day) ($\chi^2 = 11.08$, $p < 0.001$) were significantly associated with the progression to ESRD. However, there was no significant differences in age at the time of renal biopsy, male predominance, the presence of hypertension, the existence of gross hematuria, and the elevation of serum IgA between these two groups.

Histopathologic findings: The histopathologic lesions observed under light microscopy were compared between the same two groups of patients (Table 4). Class IV/V lesions under W.H.O. classification were closely associated with ESRD ($\chi^2=30.56$, $p<0.001$). Among the specific histopathologic findings, moderate to severe mesangial hypercellularity ($\chi^2=5.19$, $p<0.05$), glomerular sclerosis ($\chi^2=23.48$, $p<0.001$), interstitial infiltration ($\chi^2=18.40$, $p<0.001$), interstitial fibrosis ($\chi^2=12.84$, $p<0.001$), and tubular atrophy ($\chi^2=18.40$, $p<0.001$) were risk factors for ESRD.

Multivariate analysis of risk factors

Two clinical and six histopathological findings, identified as risk factors by univariate analysis were evaluated by multivariate analysis to assess the independent contribution to progression without any interference between them.

Using multivariate regression analysis with stepwise method, only two factors were found to influence the prognosis of IgAN significant-

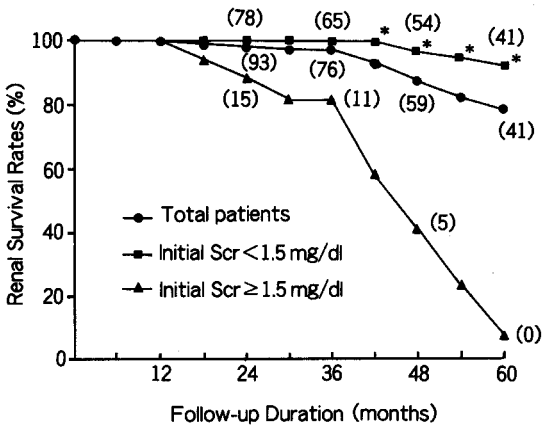

Fig. 1. *Renal Survival Rates in IgAN (Numbers in parentheses are patients at risk)*
**; p<0.01 as compared with patients who had renal insufficiency at initial presentation.*

ly (Table 5). These two independent factors were, in order of weight, class IV/V lesions under W.H.O. classification (β/SE=+6.875, p< 0.0001) and renal insufficiency at the time of presentation (β/SE=+3.915, p=0.0002).

Renal survival rates

The renal survival rates in all patients who were followed-up for more than 6 months were 100% at 1 year, 97.0% at 3 years, and 78.9% at 5 years (Fig. 1). A comparision of the renal survival rates was made between patients who had normal renal function at the time of presentation and patients who did not. The survival rates in the former were 100% at 3 years and 92.5% at 5 years. On the other hand, the survival rates in the latter were 100 % at 1 year, 81.8% at 3 years, and 7.7% at 5 years, and were significantly lower as compared to those in the former (p<0.001).

DISCUSSION

IgAN has been recognized as the most common form of primary glomerulonephritis in many countries including Japan (Hiki *et al.* 1982; Kobayashi *et al.* 1983; Chida *et al.* 1985), Singapore (Sinniah *et al.* 1976; Sinniah *et al.* 1981; Woo *et al.* 1986), France (Berger 1969; Lévy *et al.* 1985), and Italy (D'Amico *et al.* 1981; D'Amico *et al.* 1985). It has been reported that the incidence of IgAN ranges from 1.5% (Lee *et al.* 1982) to 56.2% (Sinniah *et al.* 1976) of all cases of glomerulonephritis. The reasons for this wide variation in incidence are not clear, but it may be related in part to the differ-ences in the indication for renal biopsy at various institutes as well as the influence of geographical or racial factors. In Korea, the incidence of IgAN has been reported to range from 17.8% of all cases of glomerulonephritis (Choi *et al.* 1991) to 27.5% of all the primary glomerulonephritis (Lee *et al.* 1987).

The natural course of IgAN varies in each case and is not modified according to the treatment modalities, so it is important to determine the prognostic factors for the disease. Some factors, which were already known to affect the prognosis of IgAN, are as follows; male (Hood *et al.* 1981; D'Amico *et al.* 1985; Lee *et al.* 1987), old age (Mustonen *et al.* 1985; D'Amico *et al.* 1986; Kusumoto *et al.* 1987), hypertension (Hood *et al.* 1981; Mustonen *et al.* 1985; Beukhof *et al.* 1986; D'Amico *et al.* 1986; Woo *et al.* 1986; Kusumoto *et al.* 1987; Alamartine *et al.* 1991), heavy proteinuria (Hood *et al.* 1981; Katz *et al.* 1983; Hattori *et al.* 1985; Mustonen *et al.* 1985; Beukhof *et al.* 1986; D'Amico *et al.* 1986; Woo *et al.* 1986; Alamartine *et al.* 1991), renal insufficiency at the time of presentation (Hood *et al.* 1981; Beukhof *et al.* 1986; Alamartine *et al.* 1991), high serum IgA level (Alamartine *et al.* 1991), HLA-B35 antigen (Alamartine *et al.* 1991), and severe histopathologic lesions (D'Amico *et al.* 1981; Hood *et al.* 1981; Lee *et al.* 1982; Mina and Murphy 1985; Beukhof *et al.* 1986; D'Amico *et al.* 1986; Lee *et al.* 1987; Alamartine *et al.* 1991).

In respect to the clinical and laboratory findings, 2 risk factors-heavy proteinuria and renal insufficiency at the time of presentation-were found by univariate analysis to affect the renal survival rates of IgAN in our study, and these results coincided with recent reports of the disease. But, we could not find

a better prognosis for normotensive patients that others have reported to claim as one of the favorable prognostic factors. Although there was no statistical difference in the proportion of hypertensive patients between the ESRD and the non-ESRD group, the mean diastolic pressure was significantly higher in the ESRD group (89.0 ± 18.6 mmHg vs. 81.8 ± 12.9 mmHg, $p<0.05$). Male sex, old age, and high serum IgA level have been suggested to be markers of an unfavorable prognosis. However, we observed the proportion of male patients was greater than that of female patients in the ESRD group, but when compared with the non-ESRD group, there was no difference in the sex ratio. Age and serum IgA level did not affect the renal outcome in this study.

In regard to the histopathologic findings of IgAN, there are two different classifications, one by Meadow *et al.* (1972), and the other by W.H.O. (W.H.O. classification and altas of glomerular diseases 1982). While the former is based on glomerular changes as well as tubulointerstitial lesions, the latter is based on glomerular morphology only. Even though the severity of tubulointerstitial fibrosis and tubular atrophy may reflect the severity of glomerular lesions (Sinniah 1985), there are some limitations for grading IgAN by W.H.O. criteria only. For this reason, we further studied the histopathologic findings according to not only the W.H.O. classification but also the specific histopathologic changes; mesangial hypercellularity, cellular and fibrous crescents, glomerular sclerosis (segmental or global), interstitial infiltration, interstitial fibrosis, and tubular atrophy.

D'Amico *et al.* (1981) reported that diffuse mesangial proliferation, extensive glomerular obsolescence, and severe interstitial fibrosis were more commonly observed in patients who progressed to ESRD within 5 years, and Lee *et al.* (1982) observed all patients with grade IV/V lesions according to the modified Meadow classification, developed ESRD within 3 years. Alamartine *et al.* (1991) pointed out that glomerular, tubular, interstitial, and vascular changes were more severe in the chronic renal failure (CRF) group and the global optical score (the sum of these individual changes) was a significant prognostic factor affecting the renal survival by multivariate analysis. In Asia, Chida *et al.* (1985) also reported that diffuse proliferative glomerulonephritis, diffuse proliferative glomerulonephritis with focal crescents, and glomerular deposition of IgM and/or fibrinogen-related antigen were more frequent and severe in Japanese patients whose renal function was impaired during the follow-up period. Woo *et al.* (1986) found that the presence of crescents on renal biopsy was an unfavorable long term prognostic index of IgAN in Singapore. In Korea, Lee *et al.* (1987) observed that more than 70% of the patients with high grade histopathologic lesions (Grade IV/V by modified Meadow classification) exhibited progressive renal disease, whereas patients with low grade lesions (Grade I to III) had a benign course.

In our study, we found class IV/V lesions according to W.H.O. classification served as a significant poor prognostic factor for the renal survival by multivariate analysis as well as by univariate analysis. Among the specific histopathologic changes, moderate to severe mesangial hypercellularity, glomerular sclerosis, interstitial infiltration and fibrosis, and tubular atrophy were associated with an increased risk of developing ESRD. These findings coincided with other reports (D'Amico *et al.* 1981; Hood *et al.* 1981; Lee *et al.* 1982; Mina and Murphy 1985; Beukhof *et al.* 1986; D'Amico *et al.* 1986; Lee *et al.* 1987; Alamartine *et al.* 1991).

There have been three reports concerning the prognostic factors of IgAN using multivariate analysis. Beukhof *et al.* (1986) revealed five risk factors affecting the renal outcome; heavy proteinuria, heavy microscopic hematuria, less age-adjusted glomerular filtration rate, and the absence of gross hematuria, however they did not include histopathologic data in the analysis. In the study by D'Amico *et al.* (1986), heavy proteinuria, glomerular obsolescence, interstitial fibrosis, and the extension of IgA to the peripheral capillary loop served as poor prognostic factors for CRF. In the most recent study by Alamartine *et al.* (1991), heavy proteinuria, hypertension, high

global optical score, and the presence of the HLA-B35 antigen were risk factors with a significant effect on the renal survival rates.

Compared to other reports, we also discovered that severe glomerular lesions and renal insufficiency at the time of presentation were independent risk factors of IgAN, but failed to prove heavy proteinuria as an unfavorable factor. A reason may be since we defined heavy proteinuria as a twenty-four hour urinary protein of more than 3.5 gm which was greater than the amount of 1gm used in the study by D'Amico *et al.* (1986) and 2 gm by Beukhof *et al.* (1986). In addition, our study demonstrated that heavy proteinuria correlated well with the severity of glomerular lesions ($r=+0.377$, $p<0.001$). Thus, the influence of heavy proteinuria may decrease after the first step of multivariate regression analysis.

Beukhof *et al.* (1986) calculated that 84% of 75 patients with IgAN should survive without the need of dialysis at 10 years after the first manifestation, and Alamartine *et al.* (1991) reported that the renal survival rates in 282 patients were 98% at 5 years, 94% at 10 years, 88% at 15 years, and 83% at 20 years after the onset of IgAN. In Asia, Woo *et al.* (1986) observed 91% of 151 patients had normal renal function at 6 years after their renal biopsy with no further development of renal failure up to 14 years, whereas in 86 adult patients Kusumoto *et al.* (1987) reported the renal survival rates as 80% at 10 years and 50 % at 20 years after the onset of IgAN.

In this study, the renal survival rates of IgAN using the life table method were 100% at 1 year, 97.0% at 3 years, and 78.9% at 5 years after the onset, and they were lower than those of previous studies. This outcome may be related in part to the fact that we lost too many patients during the follow-up period, and a large proportion of them were patients who were expected to have good prognosis, but did not intend to be followed up regularly because they experienced no to few symptoms.

In summary, our results show that class IV/V lesions on renal biopsy and renal insufficiency at the time of presentation are independent risk factors for the progression to ESRD, and the renal survival rate at 5 years is merely 78.9%. Considering these results, a careful follow-up will be necessary especially in patients who have either decreased renal function at the time of presentation or severe renal pathology. Furthermore, investigations on immunofluorescent and electron microscopical findings as well as HLA antigen with a large number of patients and a longer follow-up period will be needed to ascertain the prognostic factors and renal survival in Korea.

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